Single Technology Appraisal

Donanemab for treating mild cognitive impairment or mild dementia caused by Alzheimer's disease [ID6222]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Donanemab for treating mild cognitive impairment or mild dementia caused by Alzheimer's disease [ID6222]

Contents:

The following documents are made available to stakeholders:

Access the **final scope** and **final stakeholder list** on the NICE website.

1. **Company submission** from Eli Lilly & Company
   a. Submission
   b. Additional company analyses of External Assessment Report Issue 4

2. **Company summary of information for patients (SIP)** from Eli Lilly & Company

3. **Clarification questions and company responses**

4. **Patient group, professional group and NHS organisation submissions** from:
   a. Alzheimer's Research UK
   b. Alzheimer's Society
   c. Dementia UK
   d. Association of British Neurologists
   e. Faculty of Public Health
   f. Royal College of Psychiatrists
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5. **Expert personal perspectives** from:
   a. Professor Nick Fox – clinical expert, nominated by Alzheimer's Society
   b. Dr Tomas Welsh – clinical expert, nominated by RICE – The Research Institute for the Care of Older People
   c. David Thomas – patient expert, nominated by Alzheimer's Research UK
   d. Peter Almond – patient expert, nominated by Alzheimer's Research UK

6. **External Assessment Report** prepared by Southampton Health Technology Assessments Centre
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7. External Assessment Report – factual accuracy check

8. NICE Managed Access Feasibility Assessment

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

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

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

[ID6222]

Document B

Company evidence submission

19th March 2024

File name	Version	Contains confidential information	Date
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In this template any information that should be provided in an appendix is listed in a box.

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Tables and Figures

Abbreviations

Abbreviation	Definition
ACE-III	Addenbrookes Cognitive Examination-III
AChEI	Acetylcholinesterase inhibitors
AD	Alzheimer's disease
ADAMS	Aging, Demographics, and Memory Study
ADAS-Cog$_{13}$	13-Item Alzheimer's Disease Assessment Scale – Cognitive Subscale
ADCS-iADL	Alzheimer's Disease Cooperative Study – Activities of Daily Living Inventory
ADL	Activities of daily living
AE	Adverse event
AICD	Aβ intracellular domain
AMTS	Abbreviated Mental Test Score
ANCOVA	Analysis of covariance
APOE	Apolipoprotein E genotype
APP	Amyloid precursor protein
ARIA	Amyloid-related imaging abnormality
ARIA-E	Amyloid-related imaging abnormality of oedema/effusions
ARIA-H	Amyloid-related imaging abnormality of microhaemorrhages/hemosiderin deposits
Aβ	Beta-amyloid
BMI	Body mass index
BNF	British National Formulary
BSC	Best supportive care
CDR-G	Clinical Dementia Rating Global Score
CDR-SB	Clinical Dementia Rating Sum of Boxes
CI	Confidence interval
CL	Centiloid
CPEC	Care Policy and Evaluation Centre
CSF	Cerebrospinal fluid
CSR	Clinical Study Report
CT	Computed tomography
CTFβ	C-terminal fragment β
DSU	Decision Support Unit
ECG	Electrocardiogram
EES	Evaluable Efficacy Set
EQ-5D	EuroQoL 5-Dimentions
FBB	Florbetaben
FBP	Florbetapir
FDG	Fluorodeoxyglucose
GFAP	Glial fibrillary acidic protein
GPCOG	General Practitioner Assessment of Cognition

HCRU	Healthcare resource utilisation
iADRS	Integrated Alzheimer's Disease Rating Scale
IgG	Immunoglobulin G
IRC	Independent Review Charter
IQCODE	Informant Questionnaire on Cognitive Decline in the Elderly
ITT	Intention to Treat
IV	Intravenous
KOL	Key opinion leader
LS	Least squares
LSM	Least-squares mean
MCI	Mild cognitive impairment
MCID	Minimal clinically important difference
MMRM	Mixed-effect model for repeated measures
MMSE	Mini-Mental State Exam
MoCA	Montreal Cognitive Assessment
MRI	Magnetic resonance imaging
MWPC	Meaningful within-patient change
N	N-terminus
N/A	Not applicable
N3pG	N-terminal pyroglutamate modification of the third amino acid of Aβ
NCS	Natural cubic spline model
NFT	Neurofibrillary tangles
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NMDA	N-methyl-D-aspartate
PAS	Patient access scheme
PET	Positron emission tomography
PK	Pharmacokinetics
PSS	Personal social services
PSSRU	Personal Social Services Research Unit
Q4W	Every 4 weeks
QoL	Quality of life
RWE	Real-world evidence
SAE	Serious adverse event
sAPP β	Soluble amyloid precursor protein beta
SD	Standard deviation
SLR	Systematic literature review
SmPC	Summary of product characteristics
SoA	Schedule of Activities
STA	Single technology appraisal
SUVR	Standardised uptake value ratio
TEAE	Treatment emergent adverse event

UK	United Kingdom
vMRI	Volumetric magnetic resonance imaging

B.1 Decision problem, description of the technology and clinical care pathway

B.1.1 *Decision problem*

The decision problem addressed within this submission is consistent with the National Institute of Health and Care Excellence (NICE) final scope for this appraisal. The population defined in the final scope is consistent with anticipated marketing authorisation of donanemab for treating mild cognitive impairment (MCI) or mild dementia caused by Alzheimer's disease (AD). The decision problem is summarised in Table 1. The submission covers the technology's anticipated full marketing authorisation for this indication.

Table 1: The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	People with MCI or mild dementia due to AD	As per final scope	N/A
Intervention	Donanemab with or without symptomatic treatments for AD	As per final scope	N/A

Comparator(s)	Established clinical management without donanemab, including but not limited to:
	• For MCI due to AD:
	  ○ Non-pharmacological management
	• For mild dementia due to AD:
	  ○ Non-pharmacological management with or without symptomatic treatment for AD (an acetylcholinesterase inhibitor [AChEI])
		Patients were permitted symptomatic treatment with AChEIs or memantine, so established clinical management without donanemab both for MCI due to AD and mild dementia due to AD included:
		• Non-pharmacological management with or without symptomatic treatment for AD (an AChEI or memantine)
			N/A

Outcomes	The outcome measures to be considered include:
	• cognitive and functional impairment
	• non-cognitive symptoms (e.g. behavioural and psychiatric symptoms)
	• mortality
	• ability to remain independent
	• admission to full-time care
	• adverse effects of treatment
	• health-related quality of life
		The outcome measures addressed in the decision problem generally align with the final scope, with some minor differences. The outcome measures address in the submission are as follows:
		• Measures of cognition and function:
		  ○ iADRS change from baseline *(primary endpoint)*
		  ○ CDR-SB change from baseline
		  ○ ADCS-iADL change from baseline
			Data on admission to full time care and non-cognitive symptoms were not directly collected during the trial and as such are not available to present. The timeframe of the trial was too short to collect information on full time care, especially given that the patient cohort is in early stages of the disease

		○ ADAS-Cog$_{13}$ change from baseline ○ MMSE change from baseline • Biomarker-related endpoints: ○ Change in amyloid plaque deposition from baseline as measured by florbetapir F18 PET scan ○ Change in brain tau deposition from baseline as measured by flortaucipir F18 PET scan ○ Change in volumetric magnetic resonance imaging (vMRI) measures from baseline • Time-based analyses of disease progression measured with: ○ CDR-G ○ CDR-SB • Health-related quality of life: ○ QoL-AD • Adverse effects of treatment	
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to	The base case is aligned with the NICE reference case. Additional scenario analyses examining societal costs were also explored.	Caregiver informal care costs were explored in scenario analyses, in line with the following NICE guidance from the NICE health technology evaluations manual: *4.4.24. When care by family members, friends or a partner might otherwise have been provided by the NHS or PSS, it may be appropriate to consider the cost*

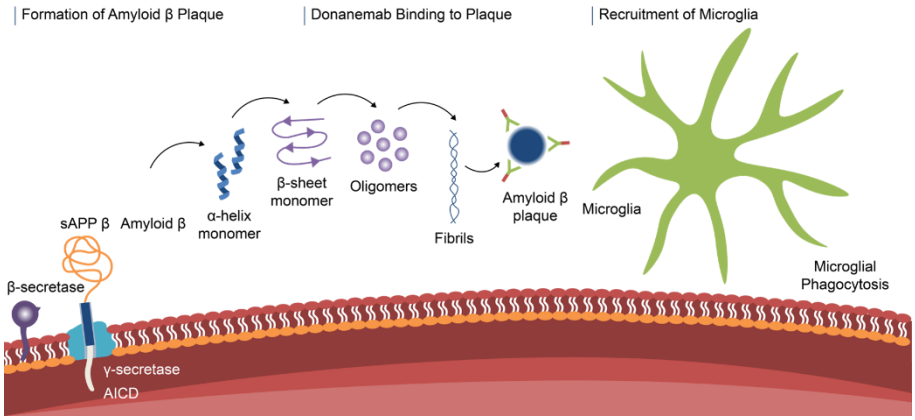
	reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from a National Health Service (NHS) and Personal Social Services (PSS) perspective. The use of donanemab is conditional on the presence of amyloid pathology. The economic modelling should include the costs associated with diagnostic testing for amyloid pathology in people with AD who would not otherwise have been tested. A sensitivity analysis should be provided without the cost of the diagnostic test. See section 4.8 of the guidance development manual (available here: https://www.nice.org.uk/process/pmg36/chapter/introduction-to-health-technology-evaluation)		*of the time of providing this care, even when adopting an NHS or PSS perspective*[1]
Subgroups to be considered	If the evidence allows the following subgroups will be considered: • Apolipoprotein E 4 (ApOE-4) gene carrier status • MCI due to AD • Mild dementia due to AD	The data presented in this submission are not presented in the subgroups outlined in the final scope. The proportion of patients entering the model in the MCI due to AD and Mild dementia due to AD health states will however be explored in scenario analyses.	The study was not powered to detect a difference in these groups and subgroup analyses suggest that these are not treatment effect modifiers.
Special considerations including issues related to equity or equality	No equality issues have been identified	As per final scope	N/A

Abbreviations: AChEI: acetylcholinesterase inhibitor; AD: Alzheimer's disease; ADAS-Cog$_{13}$: 13-Item Alzheimer's Disease Assessment Scale – Cognitive Subscale; ADCS-iADL: Alzheimer's Disease Cooperative Study – Activities of Daily Living Inventory; CDR-G: Clinical Dementia Rating – Global Score; CDR-SB: Clinical Dementia Rating – Sum of Boxes; iADRS: Integrated Alzheimer's Disease Rating Scale; MCI: mild cognitive impairment; MMSE: Mini-Mental State Exam; N/A: not applicable; NHS: National Health Service; NICE: National Institute for Health and Care Excellence; PET: positron emission tomography; PSS: personal social services; QoL-AD: Quality of Life in AD; vMRI: volumetric MRI.

B.1.2 *Description of the technology being evaluated*

A summary of the mechanism of action, marketing authorisation status, costs and administration requirements associated with donanemab for patients with MCI or mild dementia caused by AD is provided in Table 2. The draft Summary of Product Characteristics (SmPC) is presented in Appendix A.

Table 2: Technology being appraised

UK approved name and brand name	Donanemab ([redacted])
Mechanism of action	Donanemab is a humanised immunoglobulin G1 (IgG) antibody that specifically targets and binds to a truncated form of amyloid β (Aβ) – the N-terminal pyroglutamate (N3pG) epitope.[2-5] This important isoform is present only in established amyloid plaques and binding of donanemab to N3pG facilitates the removal of these plaques from the brain via microglial-mediated phagocytosis.[2-5] Selectivity of donanemab for the N3pG epitope confers no off-target binding to other Aβ species, neurotransmitters, or their receptors.[2-5] **Figure 1: Proposed donanemab mechanism of action: microglia-mediated clearance**  **Abbreviations:** Aβ: amyloid beta; AICD: Aβ intracellular domain; APP: amyloid precursor protein; CTFβ: C-terminal fragment β; N: N-terminus; N3pG: N-terminal pyroglutamate modification of the third amino acid of Aβ; sAPP β: soluble amyloid precursor protein beta. **Source:** Drolle *et al*. (2014),[6] DeMattos *et al*. (2012),[7] Kent *et al*. (2020)[8]
Marketing authorisation/CE mark status	Regulatory submission for donanemab was submitted in [redacted], and the earliest anticipated date for UK regulatory approval is [redacted].
Indications and any restriction(s) as described in the SmPC	[redacted]
Method of administration and dosage	Donanemab is administered via intravenous infusion every 4 weeks. The initial three doses are of 700 mg, titrating up to 1400 mg from the fourth dose onwards. Donanemab should be administered over at least 30 minutes and patients should be observed post-infusion for a minimum of 30 minutes. Treatment should be maintained until amyloid plaques are cleared up to a

	maximum of 18 months, or continued for 18 months if monitoring of amyloid plaque clearance with a validated method is not possible.
Additional tests or investigations	Confirmation of amyloid pathology will be required ahead of treatment initiation [redacted]
List price and average cost of a course of treatment	Donanemab is available at a list price of [redacted] per 350 mg pack. Treatment can be given for a fixed dose duration for 18 months or on a treat-to-clear regimen for up to a maximum of 18 months; both positive and negative stopping rules apply. Please see Section B.3.4.1 for further details.
Patient access scheme (if applicable)	A simple PAS is submitted for approval for donanemab. The proposed donanemab price with the PAS applied is [redacted].

Abbreviations: Aβ: beta-amyloid; AD: Alzheimer's disease; CSF: cerebrospinal fluid; IgG: immunoglobin G; MCI: mild cognitive impairment; N3pG: N-terminal pyroglutamate modification of the third amino acid of Aβ; PET: positron emission tomography; SmPC: summary of product characteristics; UK: United Kingdom.

B.1.3 *Health condition and position of the technology in the treatment pathway*

Alzheimer's disease

- AD is a progressive neurodegenerative disease, characterised by the accumulation of Aβ protein plaques and neurofibrillary tangles (NFTs) in the brain.[7, 9, 10]
- AD typically presents with memory loss, but as the disease progresses, the deficits become increasingly profound, encompassing other cognitive domains and behavioural and neuropsychiatric symptoms.[10]
- AD has a significant impact on an individual's life and those around them, as it can result in the loss of ability to perform basic activities of daily living (ADLs), such as dressing, cooking, paying bills, etc., making the individual dependent on friends, family and healthcare professionals.[11]
- In 2021, it was estimated that there were 944,000 people living with dementia in the UK, and it is estimated that there will be over 1.6 million people with dementia in the UK in 2050.[12]
- Whilst the number of people with AD is projected to increase,[12-14] the current population being assessed for this appraisal is patients with MCI due to AD or mild AD dementia, which make up a small proportion of the total dementia cases.[15]
- In 2019 it was estimated that there were 107,100 cases of mild dementia in England. As AD accounts for 50 to 75% of dementia cases in the UK,[16-18] the number of people diagnosed with mild dementia due to AD has been estimated to be around 80,000.[15, 17, 19]
- MCI is estimated to affect between 5% and 20% of the population aged 65 or over, and roughly 1 in 6 cases progress to dementia within a year.[20]
- The recent Decision Support Unit (DSU) Report (Appendix D of the NICE Health Technology Assessment [HTA] Lab Report)[21] estimates that the number of people with mild dementia in England that have presented to their healthcare provider and are suspected of AD due to clinical symptoms is approximately 73,000. They also estimate that around 62,000 of these would be expected to be amyloid positive, and would therefore be potentially eligible for amyloid-targeting therapies.[22, 23]
- The DSU also estimates that the number of people with MCI in England that have presented to their healthcare provider and are suspected of AD due to clinical symptoms is approximately 210,000. An estimate of around 100,000 of these would be expected to be amyloid positive, and would therefore be potentially eligible for amyloid-targeting therapies.[22, 23]
- Unfortunately, there is limited PET scanning capacity,[24, 25] and CSF tests are not currently widely used in the UK.[25] NICE guidance currently only recommends FDG-PET for suspected dementia, and does not recommend amyloid-sensitive PET scanning.[25, 26] Therefore, the majority of cases of AD or MCI due to AD will not have been confirmed by biomarker tests.[27, 28]

Unmet need

- The number of people living with AD is projected to increase substantially with the ageing population.[12-14]
- AD has a huge impact on the quality of life (QoL) of people living with the disease, and their families and caregivers.[10, 11]
- As symptoms progress, patients are less able to engage and function in daily activities and this can have a negative impact on psychological and physical health.[10]
- The degree of cognitive impairment has a dramatic effect on the patient's QoL and capacity to make decisions and live independently.[10] Later in the disease, people living with AD may need move into residential care facility or be cared for full-time by a friend or family member.[10, 11]
- It is predicted that, in the UK, 1.1 billion hours are spent each year on unpaid care for people with dementia.[29]
- The total costs of dementia in the UK in 2019 were £34.7 billion, of which approximately two thirds of cases are dementia due to AD.[30,15] With the prevalence of dementia predicted to increase in coming years, costs are expected to reach £94.1 billion by 2040 in the UK.[31] However, the majority of these costs will likely be driven by later stages of AD, as MCI due to AD or mild AD dementia, the focus of this submission, make up a small proportion of the total

dementia cases.[15]

- There is currently no cure for AD and no disease-modifying therapies available in the UK to slow or halt the progression of the disease.[32]

Clinical pathway of care

- Clinical practice in England is currently guided by NICE guideline NG97 (2018),[26] which outlines the recommended assessment, management and support for people living with dementia and their carers.
- There is currently no NICE guidance or current treatment options for MCI.[25]
- NG97 recommends AChEIs for mild to moderate AD and memantine for moderate to severe AD.[26] Unfortunately, these pharmacological treatments only manage the symptoms, and there is no evidence to suggest that these technologies alter the course of AD.[9]

Donanemab positioning

- Donanemab is a unique treatment which targets the underlying disease pathology, rather than only relieving symptoms.
- Donanemab is expected to be indicated for treatment initiation in patients with evidence of amyloid beta pathology and either MCI due to AD or mild AD dementia.

B.1.3.1 Disease overview

AD is an age-related progressive neurodegenerative disease, characterised by the accumulation of Aβ protein plaques and neurofibrillary tangles (NFTs) in the brain.[7, 9, 10] Other hallmarks of the disease include neuroinflammation, gliosis, neuronal loss, and synaptic changes.[33-35] Aβ deposition occurs early in the disease process, preceding tau and other pathologies and is believed to initiate the neurodegeneration cascade, clinically manifesting as cognitive and functional impairment.[7] The neuronal loss that occurs in AD is both irreversible and progressive, ultimately leading to widespread neuronal death and loss of brain tissue. AD typically presents with memory loss, but there are many associated cognitive, behavioural and neuropsychiatric features.[10] These become more profound as the disease progresses, advancing from more subtle symptoms (such as ability to manage personal finances) eventually impacting one's ability to perform basic activities of daily living (ADLs), such as cooking and dressing.[11] Alzheimer's patients are particularly vulnerable as they commonly wander, get lost and sadly may no longer recognise faces.[10, 11] The disease therefore not only has a devastating impact on the individuals themselves but has wider implications for family and friends who they become increasingly dependent upon.[11]

Disease pathophysiology

The onset of Aβ pathology, the key pathophysiological process of AD, can occur up to 20 years before the clinical onset of AD,[36-38] in what is referred to as the preclinical phase of the disease. The earliest clinical manifestations of AD can be a subjective decline in mental abilities which does not impact performance on objective cognitive tests,[10] but as the disease progresses, people living with AD show more advanced symptoms and become less independent.[10, 33]

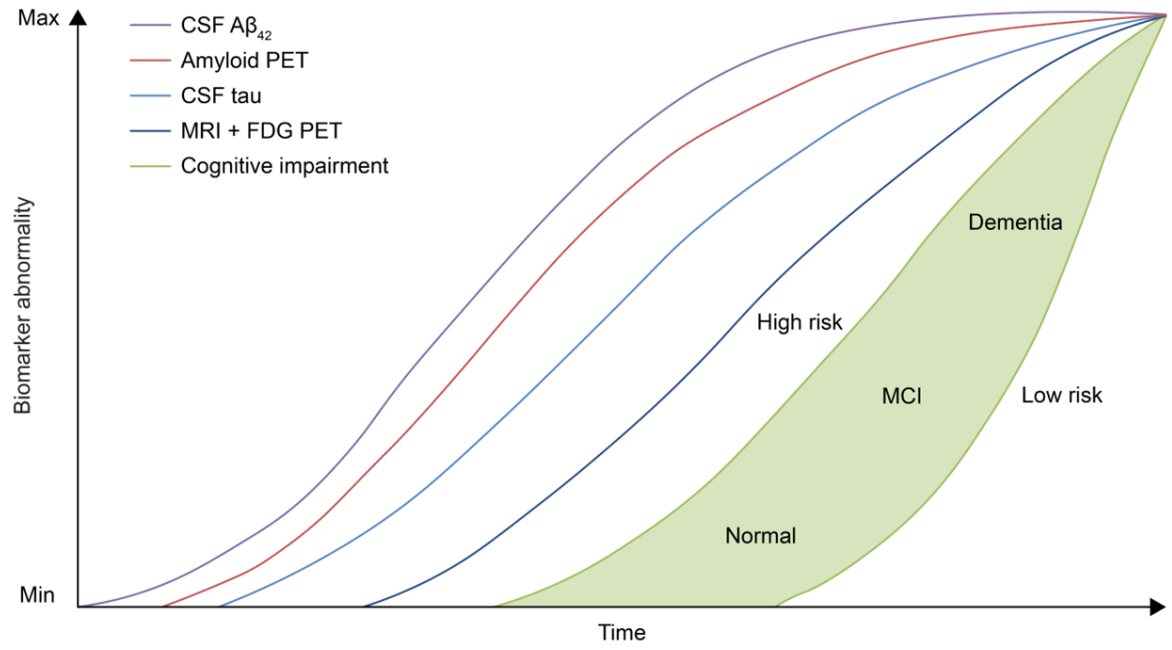
The progression of AD can be broken down into three broad stages: preclinical, MCI due to AD, and dementia due to AD.[30] Preclinical stages of the disease can last over 20 years, with studies demonstrating that changes in Aβ can occur up to 25 years before expected symptom onset.[36] MCI is the earliest symptomatic stage of cognitive impairment in which single, or potentially multiple, cognitive domains are at least mildly impaired, whilst functional capacities are relatively preserved.[10] The duration of the MCI varies greatly depending on cause, age, and other factors,[25] but estimates suggest that between 10–20% of the population aged 65 or over affected by MCI progress to dementia within 1 year.[20, 25, 39] The presence of amyloid plaques early in AD

increases the likelihood of progression from MCI to dementia AD.[4] Dementia is defined as cognitive impairment of sufficient magnitude to impair independence and affect daily life.[10, 33] The causes of dementia and MCI can vary widely and are not only caused by AD,[40] though AD is the most common cause of dementia in the UK.[16-18] Dementia and AD were the leading cause of death in the UK in 2018.[41]

There are three key stages of AD dementia; mild AD (early stage), moderate AD (middle stage) and severe AD (late stage). People aged 65 and over have an average life expectancy of 4 to 8 years after a diagnosis of AD, yet many live as long as 20 years with the disease.[42] This reflects the uncertainty in the progression of AD.[42]

The chronology of AD pathologies is represented in Figure 2, demonstrating that changes to Aβ occur early in the disease course, long before symptom development (represented in green). Changes to Aβ are first detectable in the cerebrospinal fluid (CSF) via lumbar puncture and later on PET imaging. Changes in the tau protein, cerebral structure (visible on MRI) and cerebral metabolism (detectable on FDG PET imaging) are then downstream from this.

Figure 2: Model of dynamic biomarkers of AD pathological cascade



Abbreviations: Aβ: beta-amyloid; CSF: cerebrospinal fluid; FDG: fluorodeoxyglucose; MCI: mild cognitive impairment; PET: positron emission tomography.
Source: Adapted from Jack *et al*. (2010).[43]

Epidemiology

The epidemiology of AD is entangled with that of all-cause dementia.[10] In 2021, it was estimated that there were 944,000 people living with dementia in the UK.[12] This represents 1-in-11 of the population aged 65 years and over.[12] There has been a sharp rise in the prevalence of dementia due to the ageing population,[31] and based on the current rate of prevalence it is estimated that there will be over 1.6 million people with dementia in the UK in 2050.[12] However, MCI due to AD and mild AD dementia cases, the focus of this submission, make up a small proportion of the overall dementia cases.[15]

Whilst there are approximately 944,000 people living with dementia in the UK, in 2019 it was estimated that there were 107,100 cases of mild dementia in England. As AD is the leading cause of dementia accounting for 50 to 75% of dementia cases in the UK,[16-18] the number of people diagnosed with mild dementia due to AD has been estimated to be around 80,000.[15, 17, 19] However, the majority of these cases will not have been confirmed by biomarker tests, increasing the uncertainty in the number of cases of AD.[27, 28] A recent NICE HTA Innovation Laboratory Report 'Potential Issues and Challenges in Evaluation of Disease-Modifying Dementia Treatments', was published reviewing HTA agency assessment reports and economic models of disease-modifying dementia treatments to identify challenges that may arise during evaluations of new AD treatments. A supporting report by the NICE Decision Support Unit (DSU) in Appendix D of this lab report, entitled 'Estimates of the size of the English eligible population in for amyloid targeting therapies in Alzheimer's Disease', estimated using a funnel-based approach that although the actual prevalence of mild AD will be greater than this, approximately 73,000 people with mild dementia present to a healthcare provider and are suspected of AD based on clinical symptoms. They also estimated that around 62,000 of these are expected to be amyloid positive, and therefore eligible for amyloid-targeting therapies.[22, 23]

The reported incidence and prevalence rates of MCI are heterogeneous across studies due to variation in definitions and diagnostic criteria, and so the exact number of people with MCI is unknown.[25] For example, MCI prevalence has been reported to range between <1% and 42% in older populations depending on the setting and the classification criteria used.[44] Age UK estimates that between 5% and 20% of the population aged 65 or over are affected by MCI, and that roughly 1 in 6 of these cases progress to dementia within a year.[20] Studies using magnetic resonance imaging (MRI) and PET to estimate the burden of AD have estimated that MCI with AD pathology contributes to ~50% of all cases of MCI and dementia due to AD contributes to ~60–90% of all dementia cases.[45, 46] In the aforementioned NICE HTA Lab Report Appendix D, the DSU estimate that although the actual prevalence of MCI is much greater, there are approximately 210,000 people with MCI that present to a healthcare provider and are suspected of AD based on clinical symptoms. Around 100,000 of these would be expected to be amyloid positive, and therefore potentially eligible for amyloid-targeting therapies.[22, 23]

Risk factors

The underlying cause of pathological changes in AD (Aβ, NFTs, and synaptic loss) is still unknown, but the disease has been associated with several risk factors including age, genetic factors, head injuries, vascular diseases, infections, and environmental factors.[9]

Age is the strongest risk factor for AD.[47] With advancing age, the prevalence of AD increases to an estimated 19% in individuals 75–84 years of age and to 30–35% for those older than 85 years. Other demographic risk factors for AD include gender, race and socio-economic status.[47, 48] For example, 65% of people living with dementia in the UK are women.[12] Global estimates of AD prevalence suggest that AD dementia is more prevalent in women, which is also supported by estimates that two thirds of people with Aβ-positive AD dementia are women.[49] In Europe, it is estimated that the number of women with AD is almost double that of the number of men with AD.[49]

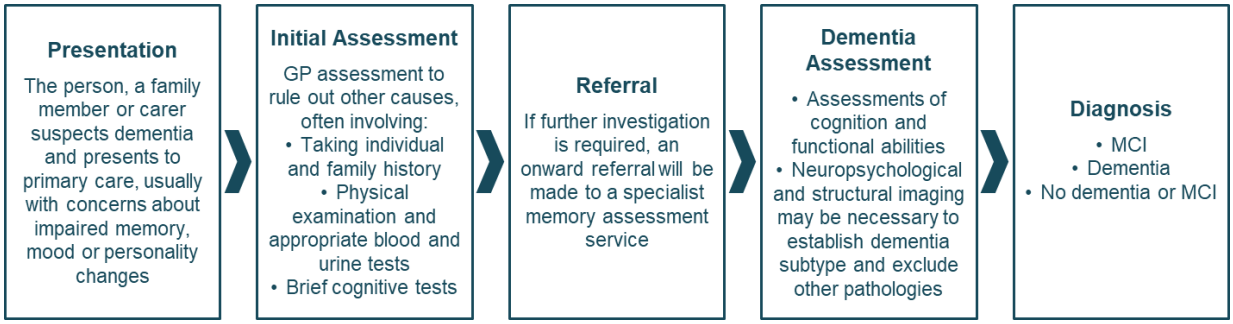
Genetic risk factors for AD include the presence of the apolipoprotein E genotype e4 allele (APOE ε4).[13] Up to 25% of the population and approximately 60-75% of AD patients in clinical studies are APOE ε4 carriers.[50] Homozygous APOE ε4 carriers have the greatest risk of developing AD, and the lowest average age of onset.[51, 52]

Diagnosis

Current diagnosis pathway

In the absence of a specific test for AD, diagnosis has historically been one of exclusion with definitive diagnosis only achievable at post-mortem. Diagnosis has focused on a combination of personal and family history, cognitive testing, and neurological examination, with blood tests and MRI or computed tomography (CT) to exclude reversable causes of cognitive decline or rule out other causes of dementia.[26, 53] If dementia is suspected, the individual is referred to a specialist dementia diagnostic service, such as a memory clinic, where further neurological examination and cognitive testing are conducted to determine the severity and subtype of dementia.[26, 54] A summary of the current dementia diagnosis pathway is presented in Figure 3.

Figure 3: Dementia diagnosis pathway



Abbreviations: GP: general practitioner; MCI: mild cognitive impairment.
Source: Adapted from National Collaborating Centre for Mental Health (2018).[55]

Cognitive assessment

Cognitive testing for dementia assesses a wide range of different mental abilities, including short- and long-term memory, concentration and attention span, language and communication skills, recall, reasoning, abstract thinking and visuospatial skills.[53, 56] Cognitive testing forms part of a wider assessment for dementia and should not be used in isolation.[56] There are a multitude of tests available, covering a broad range of settings, purposes and domains, and as such, tests vary greatly across services.[53, 54, 56] There is no specific guidance on which is the most appropriate test to use,[26] although the Alzheimer's Society cognitive assessment toolkit suggests that the cognitive assessments most appropriate for use in primary care are the Abbreviated Mental Test Score (AMTS), the General Practitioner Assessment of Cognition (GPCOG), and the Mini-Cog,[54] as they are brief and appropriate for initial assessment.[54, 56] In memory clinics, the toolkit suggests the use of the Addenbrookes Cognitive Examination-III (ACE-III), the Montreal Cognitive Assessment (MoCA), and the Mini-Mental State Examination (MMSE),.[54] which are generally more detailed and take longer to administer.[56] Additional cognitive tests include the AD8, the Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE),[52] and the Clinical Dementia Rating (CDR) scale.[40]

Importance of biomarkers in diagnosis

According to the NICE NG97 guideline for the management of dementia in the UK, if AD is suspected but the diagnosis remains uncertain after initial assessment and cognitive testing, further tests for biomarkers can be conducted.[26] Imaging modalities such as MRI and PET can be used to visualise early structural and molecular changes in the brain.[52] MRI is primarily used to exclude other causative pathologies for the cognitive impairment e.g. tumours (part of

diagnosis of exclusion).[26, 53] Evidence of temporal lobe atrophy on MRI can also contribute to an AD diagnosis.[26, 53]

PET imaging can either be used to measure the quantity of a certain protein within the brain (e.g. amyloid) or cerebral metabolism (FDG-PET). FDG-PET is a non-specific marker which measures cerebral metabolic rates of glucose as a proxy for neuronal activity, as opposed to a specific test for AD Aβ pathology.[57] Unfortunately, there is limited PET scanning capacity in the UK, with only 78 PET scanning sites.[24, 25, 58] Due to a lack of availability of amyloid-targeting therapies, NICE guidance currently only recommends FDG-PET for suspected dementia, and does not recommend amyloid-sensitive PET scanning.[25, 26] Fluid biomarker testing, such as CSF can also be used; CSF tests can measure the presence of Aβ and aggregated tau within the brain.[26, 52] CSF examination is well tolerated, less costly and less capacity-constrained than PET and is performed as part of the diagnostic process for AD in many European countries, though it is not currently widely used in the UK.[25] Lumbar punctures are however widely conducted across the UK as a routine diagnostic procedure for many other neurological conditions, including MS and meningitis.[59, 60]

With the recent emergence of novel amyloid-targeting therapies for AD, patients who are suitable for and would benefit from these will need to be accurately identified.[61] Whilst PET tracers are considered the gold standard for establishing the presence of AD pathology, they are costly and not widely accessible in some geographies. Clinical experts at the NICE Office for Market Access (OMA) multistakeholder engagement meeting for this submission agreed that CSF would be the preferred diagnostic tool for AD over PET.[62] CSF is more comprehensive as it can provide information not only on amyloid but also tau. Capacity issues for PET scanning were also discussed, and are well-understood amongst clinicians, both in terms of limited access to PET slots for non-oncology cases, as well as geographic inequities. For example, PET scanners are generally much more accessible in Southern versus Northern England. Clinicians also agreed that the cost of CSF is typically lower than PET. For these reasons, clinicians predict that there will likely be significant increase in the use of CSF for amyloid testing. However, they noted that there is a proportion of patients (10–15%) for whom CSF is not suitable that will likely still need PET for diagnosis.[62]

There are currently three amyloid-PET tracers approved in the UK by the MHRA: florbetapir (Amyvid),[63] flutemetamol (VIZAMYL)[64] and florbetaben (Neuraceq)[65]. All are indicated for PET imaging of β-amyloid neuritic plaque density in the brains of adult patients with cognitive impairment who are being evaluated for AD and other causes of cognitive impairment. [redacted]

Results of a recent study, conducted to establish the interchangeability between CSF and PET for patient identification, found that approved CSF assays are non-inferior to Aβ-PET in identifying patients with AD pathology.[66] These results support the use of CSF, which may help overcome barriers to inequitable access expected when using PET scanners for diagnosis, and therefore improve the resulting inequitable access to AD-modifying therapies.[66]

Blood biomarker tests, such as plasma tau (pTau), $A\beta_{1–42}/A\beta_{1–40,}$ neurofilament light chain (NfL) and glial fibrillary acidic protein (GFAP), have demonstrated compelling evidence for serving as a less invasive and cost-effective alternative screening measure for AD pathology.[61] There is evidence of concordance of blood-based biomarkers with amyloid PET, supporting that in future, these may be used for diagnostic testing.[67-70] This is particularly important with the emergence of

amyloid-targeting therapies such as donanemab, which will require accurate detection of amyloid pathology.[61] However, these methods still require further validation, and due to the current lack of amyloid-targeting therapies, are rarely used in practice.[10, 61] With a rise in the availability and sensitivity of blood-based biomarkers, these methods could be validated and accepted for clinical use for diagnosis and screening at earlier stages of the disease.[61] It is likely that if blood-based biomarkers were introduced either as a screening tool (rule-out) or as a 'rule-in' diagnostic test, this would be beneficial in terms of service capacity and healthcare resource use burden compared to using PET or CSF alone to identify patients with amyloid pathology.

Unmet needs in diagnosis

There is currently no NICE guidance for MCI and as MCI has, until recently, been untreatable, it is likely that this stage of the disease is underdiagnosed.[25, 26] Additionally, some cognitive testing can exhibit ceiling effects for those with milder levels of impairment, limiting patient access to an early diagnosis.[25, 26]

Diagnosis for AD is often delayed by several years after symptom onset.[71] For example, in the Aging, Demographics, and Memory Study (ADAMS), over 50% of participants meeting criteria for dementia reported no history of a clinical cognitive evaluation.[72] Patients may hide their symptoms or may incorrectly attribute symptoms to part of the normal ageing process, both of which can contribute to the delay in diagnosis.[52] Using data from surveys across Europe (specifically France, Germany, Italy, Spain, and the UK), the mean MMSE score at initial diagnosis was 21.8 (mild AD is generally defined by an MMSE score between 21–26, and moderate AD is generally defined by an MMSE score between 10–20)[73], suggesting that diagnosis is mostly occurring at the later stages of mild AD dementia rather than MCI.[74] Additionally, patients are often misdiagnosed or underdiagnosed, with up to half of patients with any form of dementia having no formal diagnosis made.[28, 75] In a study conducted in the UK, around one-third of patients diagnosed with AD had no evidence of amyloid plaques, one of the hallmarks of AD required for its neuropathological diagnosis.[27] Confirmation of amyloid plaques can provide confirmatory evidence for AD and avoid inappropriate management,[76, 77] as well as providing confirmation of eligibility for amyloid-targeting therapies.[61] Studies have demonstrated that biomarker confirmation via amyloid PET or CSF, particularly early in the diagnosis pathway, allows more frequent higher confidence diagnoses.[77-79] Early and accurate diagnosis is therefore important in guiding appropriate clinical management and improving care for the patient,[76] and will be critical for patients to benefit from amyloid-targeting therapies in the future.

B.1.3.2 Disease burden

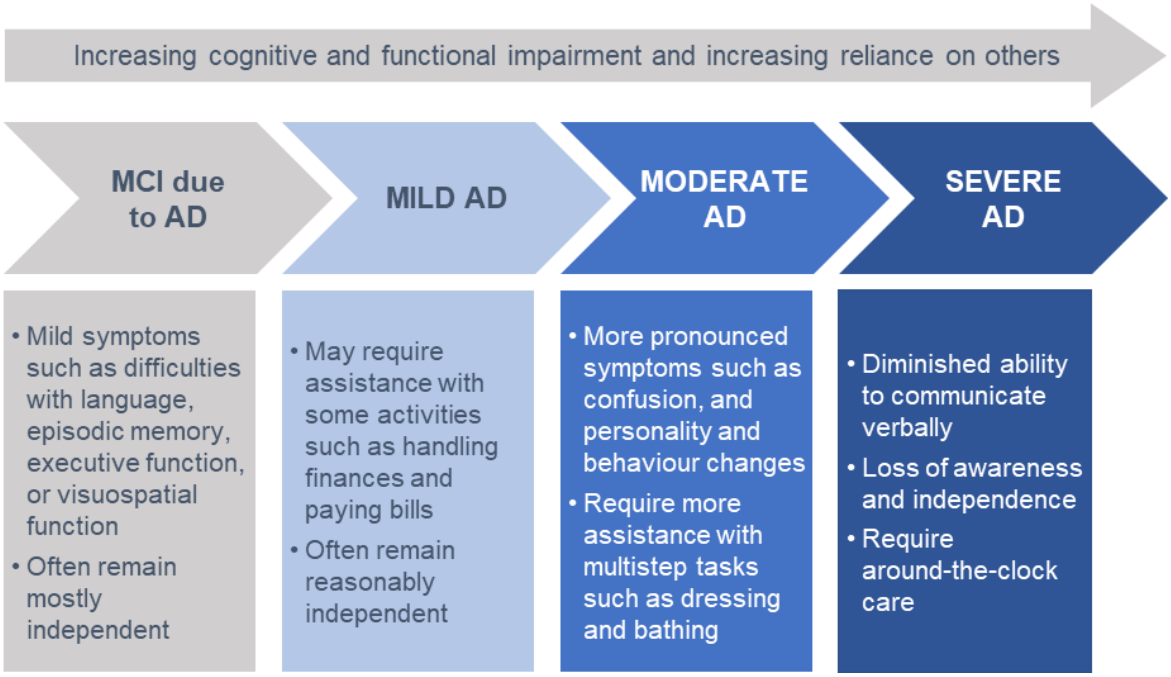
Patient burden

Due to the increase in the aging population worldwide, the number of people living with AD is projected to increase substantially,[13, 14] which will greatly impact individuals, families, and healthcare systems around the world. AD has a huge impact on the QoL of people living with the disease, and their families and caregivers.[10, 11] An AD diagnosis is often met with fear, shame and hopelessness, which can prevent people seeking medical treatment.[30] Additionally, there is currently no cure for AD and no disease-modifying therapies available in the UK to slow or halt the progression of the disease.[32] Dementia and AD were the leading cause of death in 2022, and are the only major cause of death without a treatment to prevent, slow or stop disease progression.[80, 81]

As symptoms progress, patients are less able to engage and function in daily activities and this can have a negative impact on psychological and physical health.[10] As AD affects functions like memory and cognition, it becomes more difficult to make decisions, engage in activities and socialise. This can make a person with AD feel lonely and isolated and can have a dramatic effect on a person's QoL.[11] Depression and anxiety are common and can begin to develop in the early stages of the disease, along with other changes in mood and behaviour, . [9, 10] Often, individuals will stop engaging with their hobbies and socialising with their friends, which can affect relationships, increase loneliness and decrease QoL.[11]

The degree of cognitive impairment has a dramatic effect on the patient's QoL and capacity to make decisions and live independently.[10] Later in the disease, people living with AD need extensive help in performing activities of daily living; they can wander and get lost, can be unable to manage their finances and medications, and can forget important things like appointments.[82] There is also an increase in later stages in hallucinations, delusions and behaviour changes.[83] These changes and the decreased ability to perform daily activities can make the individual vulnerable and less able to safely live alone,[82, 83] requiring the individual to be cared for full-time by a friend or family member or move into a residential specialist dementia care facility for full-time care.[10, 11] Figure 4 summarises the progression of symptoms through the stages of AD, indicating the increase in cognitive and functional impairment and reliance on others as symptoms progress.

Figure 4: Progression of symptoms through the AD continuum



Abbreviations: AD: Alzheimer's disease.
Source: Alzheimer's Association (2023);[42] Porsteinsson *et al*. (2021)[52].

AD also has an impact on physical health.[10] People with AD may have problems walking, be unsteady on their feet, find swallowing food more difficult or they may have seizures.[84] People with AD may also have problems with speaking and understanding people.[84] Changes to sleep patterns can also often occur in AD, such as waking frequently during the night.[84] Later in the disease, as symptoms get worse, physical problems are often more noticeable and patients are less able to live independently and do everyday tasks.[10, 16] They will likely need help performing

personal care tasks such as eating, washing and dressing, and there is also an increased risk of falls.[85]

It is possible, however, to maintain a good QoL in the early stages of disease. With early diagnosis and subsequent access to the right services, support and treatment, people can take control of their condition, live independently for longer, and maintain a good QoL.[30] Some studies have indicated the benefits of lifestyle and nutritional interventions, such as physical exercise, diet and bioactive compounds, as preventive strategies for the development of AD in the elderly population.[86] Overall though, there is a substantial and increasing unmet need for treatments which slow or halt the disease at early stages and prevent progression into the later stages of the disease.[30]

Caregiver burden

Most patients with AD dementia are cared for by a spouse or other family member.[87] Given the long duration of AD, the strain on carers can be lengthy.[30] In AD, the patient typically becomes dependent on the caregiver for their everyday functioning, which makes the burden on the caregiver an essential aspect of the disease. However, this burden on families and society is often not fully captured in calculations of the costs of the disease.[87] It is predicted that 1.1 billion hours are spent each year on unpaid care for people with dementia.[29]

Caring for someone with AD can be extremely challenging, due to changes in memory, behaviour and personality, including aggression in some cases.[10, 11] Caring full-time can leave family members feeling socially isolated and having to meet hidden costs.[11] Full-time caring can also impact on the caregiver's ability to continue engaging in aspects of their life such as work, resulting in loss of productivity.[87]

Caring for a person with AD can be incredibly stressful as the carer must adjust their work schedule to accommodate caring and balance the need to look after the individual with looking after themselves and other dependents.[88, 89] Additionally, carers often feel emotional stress including feelings of sadness, resentment, isolation and guilt.[88, 89] As a result of these stresses, significant levels of psychological morbidity, depression, and emotional burden are reported in care partners.[88, 89] Likely due to the complex and changing disease course along with the combined effects of increasing functional impairment and behavioural issues associated with AD,[90] care partners can experience chronic stress and substantial levels of psychological distress.[91]

B.1.3.3 Economic burden

The total costs of dementia in the UK in 2019 were £34.7 billion, of which approximately two thirds of cases are dementia due to AD[30].[15] With the prevalence of dementia predicted to increase in coming years with the rapidly ageing population, costs are expected to reach £94.1 billion by 2040 in the UK.[31]

The economic burden of dementia is divided between three main sectors: healthcare, social care and unpaid or informal care,[15, 92, 93] with the majority of costs falling on social care.[15, 31] Healthcare costs relate mainly to the NHS and are due to hospitalisation of people living with dementia,[30] and they account for 14% (£4.9 billion in 2019) of the total costs in the UK.[15] Social care costs relate to services such as nursing homes, homecare, and respite care.[30] These are privately and publicly funded and account for 45% (£15.7 billion in 2019) of the total costs in the

UK.[15] In England around 60.6% (around £8.3 billion in 2019) of the overall costs of social care are estimated to be met by service users themselves and their families.[15, 31] Informal or unpaid care costs relate to family providing unpaid care for people living with dementia,[30] and account for 40% (£13.9 billion in 2019) of total dementia care costs.[15]

It is estimated that 700,000 friends and family members care for a person with dementia in the UK.[11, 94] The dependence on the caregiver for everyday functioning can impact on the caregiver's ability to continue engaging fully in aspects of their life, such as work. The loss of productivity of people living with AD and their caregivers is one of the largest cost drivers of AD, yet value frameworks often focus on healthcare costs and ignore productivity losses.[87] The caregiver burden is generally excluded from traditional cost-effectiveness frameworks, which do not fully capture the burdens on families, economies, and society.[87]

B.1.3.4 Clinical pathway of care

Clinical practice in England is currently guided by NICE guideline NG97 (2018),[26] which outlines the recommended assessment, management and support for people living with dementia and their carers. There is currently no NICE guidance or current treatment options for MCI.[25]

Three AChEIs, donepezil, galantamine and rivastigmine monotherapies, are recommended as options for managing mild to moderate AD in the NG97 guideline.[26] The N-methyl-D-aspartate (NMDA) receptor antagonist memantine monotherapy is also recommended as an option for managing AD for people with:

- moderate AD who are intolerant of or have a contraindication to AChEIs **or**
- severe AD

In clinical practice, these therapies may be used earlier in the clinical treatment pathway than NG97 recommends, due to the limited treatment options available, particularly for MCI. For example, a recent Adelphi survey reported that [redacted] MCI patients used off-label AChEI and [redacted] patients with mild AD dementia used AChEI. Additionally, in different countries, these therapies may be used earlier in the clinical pathway. These treatments currently only manage the symptoms, and there is no evidence to suggest that these technologies alter the course of AD.[9]

Non-pharmacological treatment of AD includes social support, increasing assistance with day-to-day activities, information and education, carer support groups, community dementia teams, home nursing and personal care, community services such as meals-on-wheels, befriending services, day centres, respite care and care homes.[73] Some studies have also indicated the benefits of lifestyle and nutritional interventions, such as physical exercise, diet and bioactive compounds, as preventive strategies for the development of AD in the elderly population.[86, 95] In addition to targeting lifestyle risk factors, there is evidence that optimising medical treatment of comorbidities, such as diabetes and cardiovascular health, can aid in the prevention of AD.[96]

Proposed positioning of donanemab

Donanemab is a treatment which targets the underlying disease pathology in AD, rather than simply relieving symptoms. Currently, there are no other amyloid-targeting treatments available to patients. Donanemab is expected to be indicated for the management of MCI due to AD or mild AD dementia.

B.1.4 *Equality considerations*

No equality issues have been identified.

B.2 Clinical effectiveness

Clinical Effectiveness Summary

TRAILBLAZER-ALZ 2 trial

- The efficacy and safety of donanemab for the treatment of AD in patients with MCI due to AD or mild AD dementia were evaluated in an 18-month phase 3 randomised double-blind placebo-controlled trial (TRAILBLAZER-ALZ 2). The trial included 1,736 participants, 860 received donanemab and 876 received a placebo
- The primary efficacy endpoint was change from baseline in the Integrated AD Rating Scale (iADRS) score at 76 weeks, a composite score assessing both cognitive and functional ability
- Key secondary endpoints included change from baseline at 76 weeks in the Clinical Dementia Rating Sum of Boxes (CDR-SB), the Alzheimer's Disease Cooperative Study – Activities of Daily Living Inventory (ADCS iADL) and the 13-Item Alzheimer's Disease Assessment Scale – Cognitive Subscale ($ADASCog_{13}$) scores. A percentage of slowing of clinical progression was calculated for key endpoints
- Additional secondary outcomes included amyloid plaque reduction at 76 weeks, percentage of participants reaching amyloid clearance (<24.1 Centiloids as measured by amyloid PET) at 24 weeks and 76 weeks, tau PET (frontal cortical regions) change, vMRI (whole brain, hippocampus, and ventricles) change, and adverse events
- Amyloid-related imaging abnormalities (ARIA) of oedema/effusion (ARIA-E) and of microhaemorrhages and hemosiderin deposits (ARIA-H), and infusion-related reactions (IRR) were adverse events (AE) of special interest

Summary of efficacy

- The TRAILBLAZER-ALZ 2 trial demonstrated that donanemab significantly slowed cognitive and functional decline, providing an important replication of the successful phase 2 study. The effect was consistent across all cognitive and functional endpoints tested, regardless of the statistical model used.
- Donanemab treatment resulted in clinically meaningful benefit (considered to be >20% slowing of clinical progression){{Sims, 2023 #18}} on the iADRS and CDR-SB scales, which resulted in 22.3% and 28.9% slowing of clinical decline, respectively.
- In addition to slowing cognitive and functional decline, donanemab treatment resulted in significantly reduced brain amyloid plaque burden in participants as early as six months and at all time points assessed, with 76% of participants in the overall population achieving amyloid clearance at 76 weeks

Summary of safety

- The safety profile of donanemab was similar to that seen in the phase 2 trial, TRAILBLAZER-ALZ. ARIA AEs were observed in keeping with class effects associated with amyloid plaque-lowering therapies
- ARIA led to serious outcomes for 1.6% of participants on donanemab, requiring hospitalisation, supportive care and/or corticosteroid use and three participants with serious ARIA subsequently died. None of these three individuals received concomitant anticoagulant or antiplatelet therapy
- The majority of ARIA events were however asymptomatic, and mild to moderate radiographically (93%). 52 participants had symptomatic ARIA-E, and 45 of these (86.5%) had symptom resolution within 72.4 days. When ARIA-E symptoms did occur they were usually mild, consisting of headache or confusion, but more severe symptoms such as seizures were observed in some participants

Conclusion

- In a disease lacking an available disease-modifying therapy in the UK, donanemab significantly slowed clinical progression of AD at 76 weeks compared to placebo with improvements seen consistently across all cognitive and functional endpoints tested, regardless of statistical model
- Donanemab will therefore help to address the high unmet need experienced by patients with MCI due to AD and mild AD dementia, and allow patients to spend longer in less severe stages of the disease

B.2.1 *Identification and selection of relevant studies*

A clinical systematic literature review (SLR) was conducted in June 2023, and subsequently updated in August 2023, to identify relevant clinical evidence on the clinical efficacy and safety outcomes in patients with AD. The SLR was designed to capture data specifically in AD reported in both interventional (RCT and non-RCT) and observational studies, and considered baseline characteristics as relevant outcomes, in addition to efficacy and safety and QoL data. The SLR was conducted according to a pre-specified protocol and performed in accordance with established guidelines (i.e., Preferred Reporting Items for Systematic Reviews and Meta-analyses [PRISMA] and the Cochrane Handbook for Systematic Reviews of Interventions)[100, 101] as well as the standards required by the NICE.

In total, the SLR identified 39 relevant publications reporting on 14 unique studies that met the inclusion criteria of the review.

Full details of the SLR search strategy, study selection process and results are presented in Appendix B.

B.2.2 *List of relevant clinical effectiveness evidence*

As described above the SLR identified 14 interventional studies. Of the 14 studies considered for full extraction, only three trials (TRAILBLAZER-ALZ, TRAILBLAZER-ALZ 2, and TRAILBLAZER-ALZ 4) provide evidence for the clinical efficacy and safety of donanemab in the patient population of interest for this appraisal (patients with MCI due to AD or mild AD dementia).

- TRAILBLAZER-ALZ is a phase 2 trial, which although is relevant to this submission, did not inform the cost effectiveness analyses. The results of this trial are presented in Appendix I.1
- TRAILBLAZER-ALZ 2 is a phase 3 trial which provides the main efficacy and safety data that inform the cost effectiveness analyses with this submission. Results from TRAILBLAZER-ALZ 2 are presented in Section B.2.6
- TRAILBLAZER-ALZ 4, a phase 3 trial comparing donanemab with aducanumab, is not considered relevant to this submission as it compares donanemab with a treatment that is not approved for use in the UK and is therefore not used in NHS clinical practice. Results from this trial are due to be published in March 2024
- Safety data presented within this submission include an integrated dataset including data from the TRAILBLAZER-ALZ, TRAILBLAZER-ALZ 2 and TRAILBLAZER-ALZ 4 trials, in addition to separate safety data from the TRAILBLAZER-ALZ 2 trial. These safety data are presented in Section B.2.10

Full details of the SLR are presented in Appendix B.

TRAILBLAZER-ALZ 2

The main body of evidence to address the decision problem is derived from the TRAILBLAZER-ALZ 2 trial, which was used to support the marketing authorisation for donanemab in the indication of relevance to this submission. TRAILBLAZER-ALZ 2 is a phase 3 randomised double-blind placebo-controlled 18-month trial assessing the efficacy and safety of donanemab, an antibody designed to clear brain amyloid plaque, in participants with early symptomatic AD

(MCI due to AD or mild AD dementia). An overview of TRAILBLAZER-ALZ 2 is presented in Table 3 and the methodology and results are presented below.

Table 3: Clinical effectiveness evidence

Study	**TRAILBLAZER-ALZ 2 (NCT04437511)**
Study design	A 76-week, phase 3, randomised, double-blind, parallel, multicentre, placebo-controlled trial to assess the efficacy and safety of donanemab in participants with early symptomatic AD (MCI due to AD or mild AD dementia) with evidence of amyloid and tau pathologies
Population	Participants aged 60 to 85 years with early symptomatic AD (MCI due to AD or mild AD dementia).
Intervention(s)	Donanemab (700 mg for the first 3 doses and 1400 mg thereafter) administered intravenously every 4 weeks for up to 72 weeks.
Comparator(s)	Placebo
Indicate if study supports application for marketing authorisation	Yes
Indicate if study used in the economic model	Yes
Rationale if study not used in model	N/A

Reported outcomes specified in the decision problem (outcomes in bold are incorporated into the model base-case)	• Measures of cognition and function:
	  ○ iADRS change from baseline (primary endpoint)
	  ○ **CDR-SB change from baseline**
	  ○ ADCS-iADL change from baseline
	  ○ ADAS-Cog$_{13}$ change from baseline
	  ○ MMSE change from baseline
	• Biomarker-related endpoints:
	  ○ **Change in amyloid plaque deposition from baseline as measured by florbetapir F18 PET scan**
	  ○ Change in brain tau deposition from baseline as measured by flortaucipir F18 PET scan
	  ○ Change in volumetric magnetic resonance imaging (MRI) measures from baseline
	• Health-related quality of life:
	  ○ QoL-AD

All other reported outcomes (outcomes in bold are incorporated into the model base-case)	Safety measures:
	• **Spontaneously reported adverse events (AEs)**
	• **MRI (ARIA and emergent radiological findings)**
	Exploratory outcomes:
	• Time-based analyses:
	  ○ CDR-G
	  ○ CDR-SB

Abbreviations: AD: Alzheimer's disease; ADAS-Cog$_{13}$: 13-item Alzheimer's Disease Assessment Scale – Cognitive Subscale; ADCS-ADL: Alzheimer's Disease Cooperative Study – Activities of Daily Living; AE: adverse event; ARIA: amyloid-related imaging abnormalities; CDR-G: Clinical Dementia Rating Scale Global Score; CDR-SB: Sum of Boxes of the Clinical Dementia Rating Scale; iADRS: Integrated AD Rating Scale; MCI: mild cognitive impairment; MMSE: Mini-Mental State Examination; N/A: not applicable; PET: positron emission tomography; QoL-AD: Quality of Life in AD; vMRI: volumetric MRI.
Source: Sims *et al.* (2023)[5]

TRAILBLAZER-ALZ

The TRAILBLAZER-ALZ trial provides supporting evidence for the decision problem and is of relevance to this submission. TRAILBLAZER-ALZ is a phase 2 randomised double-blind placebo-controlled trial assessing the safety, adverse events, and efficacy of donanemab, in participants with early symptomatic AD. An overview of TRAILBLAZER-ALZ is presented in Table 4, with results presented in Appendix I.1.

Table 4: Clinical effectiveness evidence

Study	**TRAILBLAZER-ALZ (NCT03367403)**
Study design	A 76-week, phase 2, randomised, double-blind, parallel, multicentre, placebo-controlled trial to assess the safety, adverse events, and efficacy of donanemab in participants with early symptomatic AD (MCI due to AD or mild AD dementia) with amyloid and tau pathologies.
Population	Participants aged 60 to 85 years with early symptomatic AD (MCI due to AD or mild AD dementia).
Intervention(s)	Donanemab (700 mg for the first 3 doses and 1400 mg thereafter) administered intravenously every 4 weeks for up to 72 weeks.
Comparator(s)	Placebo
Indicate if study supports application for marketing authorisation	Yes
Indicate if study used in the economic model	No
Rationale if study not used in model	This phase 2 study provides supporting evidence for the submission but is not included in the model, as results from larger phase 3 study are used.

Reported outcomes specified in the decision problem	• Measures of cognition and function:
	  ○ iADRS change from baseline (primary endpoint)
	  ○ CDR-SB change from baseline
	  ○ ADCS-iADL change from baseline
	  ○ ADAS-Cog$_{13}$ change from baseline
	  ○ MMSE change from baseline

	• Biomarker-related endpoints:
	  ○ Change in amyloid plaque deposition from baseline as measured by florbetapir F18 PET scan
	  ○ Change in brain tau deposition from baseline as measured by flortaucipir F18 PET scan
	  ○ Change in volumetric magnetic resonance imaging (MRI) measures from baseline

All other reported outcomes	Safety measures: • Spontaneously reported adverse events (AEs) • MRI (ARIA and emergent radiological findings)

Abbreviations: AD: Alzheimer's disease; ADAS-Cog$_{13}$: 13-Item AD Assessment Scale – Cognitive subscale; ADCS-ADL: Alzheimer's Disease Cooperative Study – Activities of Daily Living Scale; AE: adverse event; ARIA: amyloid-related imaging abnormalities; CDR-G: Clinical Dementia Rating Global Score; CDR-SB: Clinical Dementia Rating Sum of Boxes; iADRS: Integrated AD Rating Scale; MCI: mild cognitive impairment; MMSE: Mini-Mental State Exam; N/A: not applicable; PET: positron emission tomography; QoL-AD: Quality of Life in AD; vMRI: volumetric MRI.
Source: Mintun *et al*. (2021)[4]

B.2.3 *Summary of methodology of the relevant clinical effectiveness evidence*

B.2.3.1 Neuropsychological tests in the TRAILBLAZER-ALZ 2 trial

There are many neuropsychological tests available for measuring disease severity and progression of MCI due to AD and mild AD dementia, however no single test is recognised as the gold standard, as discussed in Section B.1. A summary of the neuropsychological tests used in the TRAILBLAZER-ALZ 2 trial and their associated meaningful within-patient change (MWPC) values is given in Table 5.

Table 5. Neuropsychological Tests

Scale	Range	Score direction with greater disease severity	MWPC*		Additional information
			MCI due to AD	Mild dementia due to AD	
ADAS-Cog$_{13}$	0–85	Higher	2	Not available	• Rater-administered, answered by participant/includes items rated by clinician • Assessment of cognition
ADCS-iADL	0–59	Lower	Not available	Not available	• A subset of the ADCS-ADL scale • Rater-administered, answered by participant study partner • Assessment of function
CDR-SB	0–18	Higher	1	2	• Semi-structured interview with participant and study partner/clinician rated

					• Integrated assessment of cognition and daily function
CDR-G	0–3	Higher	No MWPC thresholds defined as any change indicates a change in disease stage and is therefore meaningful.	No MWPC thresholds defined as any change indicates a change in disease stage and is therefore meaningful.	• Semi-structured interview with participant and study partner/clinician rated • *Clinical Staging instrument. Stages*: 0=normal, 0.5=very mild dementia, 1=mild dementia, 2=moderate dementia, 3=severe dementia
iADRS	0–144	Lower	–5	–9	• Mathematical derivation based on scores obtained from the ADAS-Cog$_{13}$ and ADCS-iADL • Integrated assessment of cognition and daily function
MMSE	0–30	Lower	–1	–2	• Rater-administered, answered by participant • Assessment of cognition

Footnotes: *Further detail on MWPC is provided in the section below.
Abbreviations: AD: Alzheimer's Disease; ADAS-Cog: Alzheimer's Disease Assessment Scale- Cognitive Subscale; ADAS-Cog$_{13}$: 13-Item Alzheimer's Disease Assessment Scale – Cognitive subscale; ADCS-iADL: Alzheimer's Disease Cooperative Study – Instrumental Activities of Daily Living Inventory; CDR: Clinical Dementia Rating; CDR-SB: Clinical Dementia Rating–Sum of Boxes; iADRS: Integrated Alzheimer's Disease Rating Scale; MCI: Mild Cognitive Impairment; MMSE: Mini-Mental State Examination; MWPC: meaningful within patient change.
Source: Sims *et al.* (2023).[5]

Meaningful within-patient change

MWPC is a change that occurs in an individual patient over time, and when appropriately applied, MWPC measures offer a patient-centric perspective in clinical trials. However, outcome measures used to calculate current MWPC may not be aligned with what matters most to patients.[102] Where available, MWPC values for each of the neuropsychological tests is provided in Table 5.

MWPC metrics are frequently misapplied to between-group comparisons which are commonly used to evaluate treatment effect. MWPC differs from between-group differences, as these measure the difference between two trial arms and do not provide information on the magnitude of change experienced by an individual.[103] [104] If MWPC estimates are applied to between-arm change, they are best reserved for symptomatic treatments in which the drug-placebo difference remains constant.[105] Donanemab, as a potential disease-modifying therapy, produces progressively divergent drug and placebo trajectories (see data presented in Section B.2.6).[105] Early in the trial the MWPC would therefore not be expected to be achieved, however, later the MWPC may well be achieved or exceeded.[105]

However, challenges and uncertainties surround MWPC estimation and application due to the lack of a universally accepted standard, variations in calculation methods, threshold values, and misinterpretations for group-level versus individual-level changes. Specifically, MWPC estimates

may vary as a function of calculation method employed, time periods evaluated and characteristics of the patient population.

Within this submission, >20% slowing of progression has been taken to be clinically meaningful.{{Sims, 2023 #18}} Slowing of the disease initiated in the earlier stages could mean more time in the less impaired and more functional stages of AD, as well as a delay in the onset of a later, more severe, stage – see Section B.2.6.2 for time-based analyses, which translate statistical significance into patient-relevant outcomes.

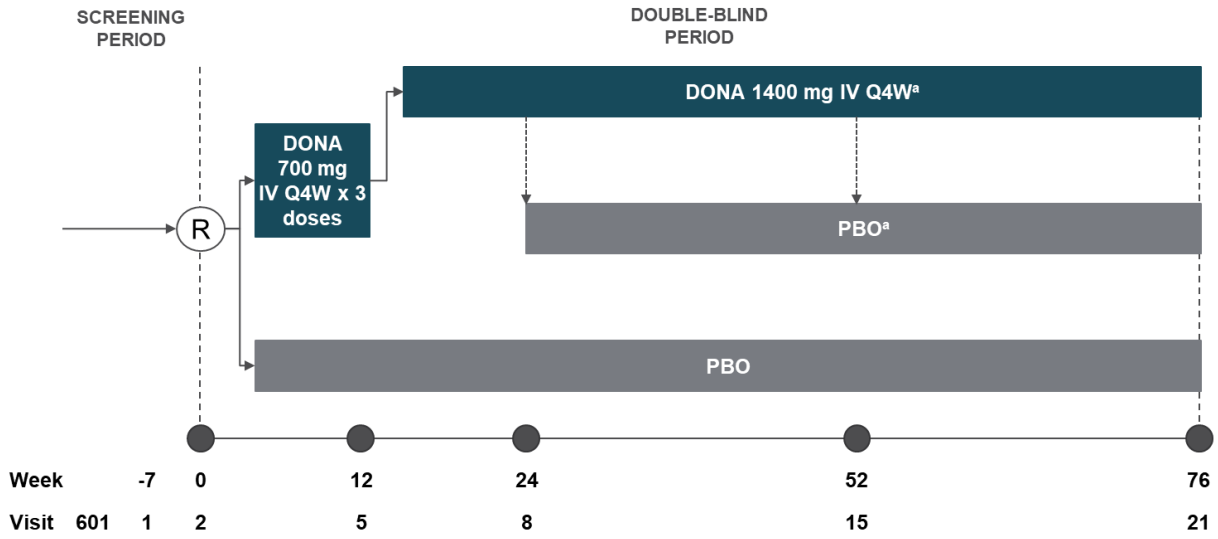
B.2.3.2 Trial design

TRAILBLAZER-ALZ 2 was a 76-week, phase 3, randomised, double-blind, parallel, multicentre, placebo-controlled trial to assess the efficacy and safety of donanemab in participants with early symptomatic AD (MCI due to AD/mild AD dementia). Participants who met entry criteria were randomised in a 1:1 ratio to one of the following treatment groups:

- Donanemab: 700 mg IV every 4 weeks (Q4W) for first 3 doses and then 1400 mg IV Q4W
- Placebo

A summary of the trial design of TRAILBLAZER-2 is presented in Figure 5.

Figure 5: Study design of TRAILBLAZER-ALZ 2



[a]Dosing decisions are based on reduction in amyloid burden as determined by the florbetapir F18 PET scan at Weeks 24, 52 and 76.
Notes: V601 is optional. For participants who do not complete V601, the procedures will be included in V1. Randomisation occurs at V2.
Abbreviations: IV: intravenous; PET: positron emission tomography; Q4W: every 4 weeks; V: Visit.
Source: Sims *et al*. (2023).[5]

Amyloid plaque reduction was measured by florbetapir F18 PET scans at Visit 8 (Week 24), Visit 15 (Week 52), Visit 21 (Week 76), or Visit 28 (Week 102) or Visit 35 (Week 130) in the extension period. If amyloid plaque level was <11 Centiloids on any single PET scan or <25 but ≥11 Centiloids on 2 consecutive PET scans, participants could complete treatment and step down from donanemab to placebo, in a double-blinded process. Participant randomisation was stratified by investigative site and tau pathology (low–medium versus high). Final adverse events and efficacy assessments were performed at 76 weeks.

ARIA monitoring occurred with scheduled MRIs at Week 4, 12, 24, 52, and 76 and unscheduled MRIs at investigator discretion. Any participant with detected ARIAs had imaging every 4 to 6 weeks until resolution or stabilisation.

After 76 weeks, participants were assigned to donanemab or placebo in a 78-week extension period.

- Participants randomised to donanemab during the double-blind period who do not meet the treatment completion criteria by visit 21 continue receiving donanemab.
    - Participants who remained on 700 mg during the double-blind period have the opportunity to dose escalate to 1400 mg at visit 25 or after.
- Participants randomised to donanemab during the double-blind period who meet treatment completion criteria by visit 21 are assigned to receive placebo starting at visit 22.
- Participants randomized to placebo during the double-blind period are assigned to receive donanemab starting at visit 22 and follow the same dose titration as participants during the double-blind period.

The maximum total duration of study participation for each participant, including screening and the post-treatment follow-up periods, is up to 205 weeks. For those entering the extension who have not reached treatment completion criteria during the double-blind phase, the maximum duration of treatment is 150 weeks. This is not expected to reflect the licenced posology.

Participant randomisation was stratified by tau pathology (low-medium versus high) and both the low-medium tau and overall populations were primary analysis populations in the study. Elevated tau was used as an enrichment criterion in the phase 3 trial to show benefit of the treatment in a trial of 18-month duration. However, treatment is unlikely to extend beyond this period in clinical practice and the company does not anticipate the need to identify patients with tau pathology for initiation of treatment, as donanemab is an amyloid-targeting therapy. Inclusion of the low--medium tau population, the population assessed in the phase 2 trial, was to enable confirmation and expansion of the results from the phase 2 trial. The results for the overall population are presented in the main text of this appraisal, and the results for the low-medium tau population can be found in Appendix C.

B.2.3.3 Trial methodology

A summary of the methodology of TRAILBLAZER-ALZ 2 is presented in Table 6 below.

Table 6: Summary of the methodology of TRAILBLAZER-ALZ 2

Trial name	TRAILBLAZER-ALZ 2
Location	277 sites in 8 countries: US, Australia, Canada, Czech Republic, UK, Japan, the Netherlands, and Poland.
Trial design	A 76-week, phase 3, randomised, double-blind, parallel, multicentre, placebo-controlled trial to assess the efficacy and safety of donanemab, an antibody designed to clear brain amyloid plaque, in participants with early symptomatic AD (MCI due to AD or mild AD dementia) with amyloid and tau pathologies
Eligibility criteria for participants (please see	**Key inclusion criteria** • 60–85 years of age (inclusive) • Capable of giving signed informed consent

Appendix I.2.1 for the full list of criteria)	• Gradual and progressive change in memory function reported by the participant or informant for ≥6 months • An MMSE score of 20 to 28 (inclusive) at Visit 601 or 1 • Meet flortaucipir/florbetapir F18 scan criteria (as detailed in Appendix I.2.1) • Have a study partner who will provide written informed consent to participate, is in frequent contact with the participant and will accompany the participant to study visits or be available by telephone • Have adequate literacy, vision, and hearing for neuropsychological testing • Stable concomitant symptomatic AD medications and other medication that may impact cognition for at least approximately 30 days prior to randomisation **Key exclusion criteria** • Significant neurological disease affecting the central nervous system other than AD • Current serious or unstable illnesses • History of cancer within the last 5 years • Participants with any current primary psychiatric diagnosis other than AD if the psychiatric disorder or symptom is likely to confound interpretation of drug effect, affect cognitive assessment, or affect the participant's ability to complete the study • Have any contraindications for MRI, including claustrophobia or the presence of contraindicated metal (ferromagnetic) implants/cardiac pacemaker • Contraindication to PET • Have any clinically important abnormality at screening, as determined by investigator, in physical or neurological examination, vital signs, ECG, or clinical laboratory test results that could be detrimental to the participant, could compromise the study, or show evidence of other aetiologies for dementia • Have a centrally read MRI demonstrating presence of ARIA-E, >4 cerebral microhaemorrhages, more than 1 area of superficial siderosis, any microhaemorrhage or severe white matter disease at screening • Have had prior treatment with a passive anti-amyloid immunotherapy <5 half-lives prior to randomisation • Have received active immunisation against Aβ in any other study
Intervention	• After confirmation of the eligibility criteria, patients were randomised 1:1 to receive up to 72 weeks of treatment with donanemab or placebo during the double-blind period • Participants in the donanemab arm received 700 mg intravenous (IV) Q4W for the first 3 doses and then 1400 mg IV Q4W
Method of study drug administration	**Donanemab** • Administered by IV infusion over a minimum of 30 minutes • Administered once Q4W and could not be administered at a dosing interval of <21 days at any time in the study **Placebo** • Administered by IV infusion Q4W

Permitted and disallowed concomitant medication	• Use of approved or standard of care symptomatic treatments for AD was permitted during the study, provided that the dose had been unchanged for at least approximately 30 days before randomisation • When medically indicated, initiation, increase or discontinuation of symptomatic treatments for AD was permitted • Nonmedication treatments for AD such as behavioural management were permitted but were subject to the same restrictions as medication treatment taken for AD • IgG therapy was not allowed during the study
Primary outcomes	Change from baseline in iADRS score through to Week 76 in: • the low–medium tau pathology population **or** • the overall population

Secondary and exploratory outcomes	**Key secondary efficacy endpoints**
	• Change from baseline through Week 76 in at least one of:
	  ○ the low–medium tau pathology population or
	  ○ the overall population
	as measured by:
	  ○ CDR-SB
	  ○ ADAS-Cog$_{13}$ score
	  ○ ADCS-iADL score
	  ○ MMSE score
	• Change in brain amyloid plaque deposition from baseline through Week 76 as measured by florbetapir F18 PET scan
	• Change in brain tau deposition from baseline through Week 76 as measured by flortaucipir F18 PET scan
	• Change in volumetric MRI measures from baseline through Week 76
	
	Safety assessments
	• Spontaneously reported AEs
	• Clinical laboratory tests
	• Vital sign and body weight measurements
	• 12-lead ECGs
	• Physical and neurological examinations
	• MRI (ARIA and emergent radiological findings)
	• Infusion related reactions
	• C-SSRS
	
	Pharmacokinetic (PK) assessments
	• Plasma PK of donanemab
	• Anti-drug antibodies (ADAs) against donanemab including:
	  ○ treatment-emergent ADAs
	  ○ neutralizing antibodies

Duration of study and follow-up	Enrolment began 19th June 2020, and ended 5th November 2021, and database lock/unblinding (double blind phase) occurred on 28th April 2023.

Abbreviations: AD: Alzheimer's disease; ADA: anti-drug antibody; ADAS-Cog$_{13}$: 13-item Cognitive Subscale of the Alzheimer's Disease Assessment Scale; ADCS-iADL: Alzheimer's Disease Cooperative Study–Instrumental Activities of Daily Living Inventory; AE: adverse event; ARIA-E: amyloid-related imaging abnormality of oedema/effusions; CDR-SB: Clinical Dementia Rating Scale-Sum of Boxes; ECG: electrocardiogram; iADRS: integrated Alzheimer Disease Rating Scale; IgG: immunoglobin G; MMSE: Mini-Mental State Exam; MRI: magnetic resonance imaging; PET: positron emission tomography; PK: pharmacokinetic; Q4W: every 4 weeks; US: United States.
Source: Sims *et al.* (2023)[5]

B.2.3.4 Baseline characteristics

Baseline demographics and clinical characteristics of the overall population of patients with AD included in TRAILBLAZER-ALZ 2 are presented in Table 7.

Table 7: Baseline demographics and clinical characteristics in the overall population[a]

Characteristics	Overall population	
	Donanemab (n=860)	Placebo (n=876)
Sex, n (%)		
Women	493 (57.3)	503 (57.4)
Age, mean (SD), y	73.0 (6.2)	73.0 (6.2)
Race, n (%)[b]		
American Indian or Alaska Native	2 (0.2)	0
Asian	57 (6.6)	47 (5.4)
Black or African American	19 (2.2)	21 (2.4)
White	781 (90.9)	807 (92.1)
Multiple	0	1 (0.1)
Missing	1 (0.1)	0
Race (US only), n/N (%)[b]		
American Indian or Alaska Native	2/619 (0.3)	0
Asian	8/619 (1.3)	3/632 (0.5)
Black or African American	18/619 (2.9)	16/632 (2.5)
White	591/619 (95.5)	612/632 (96.8)
Multiple	0	1/632 (0.2)
Ethnicity (US only), n (%)[c]		
Hispanic/Latino	35 (5.7)	36 (5.7)
Not Hispanic/Latino	583 (94.3)	594 (94.3)
Education of ≥13 y, n (%)	606 (70.5)	637 (72.8)
APOE carrier, n (%)	598 (69.8)	621 (71.2)
E2/E2	0	1 (0.1)
E2/E3	18 (2.1)	20 (2.3)
E2/E4	22 (2.6)	25 (2.9)
E3/E3	241 (28.1)	230 (26.4)
E3/E4	433 (50.5)	450 (51.6)

Characteristics	Overall population	
	Donanemab (n=860)	Placebo (n=876)
E4/E4	143 (16.7)	146 (16.7)
Acetylcholinesterase inhibitor/memantine use, n (%)	521 (60.6)	538 (61.4)
Clinical outcomes, mean (SD)[d]		
iADRS score	104.1 (14.3)	103.6 (14.0)
CDR-SB score	4.0 (2.1)	3.9 (2.1)
ADAS-Cog$_{13}$ score	28.7 (8.8)	29.3 (8.9)
ADCS-ADL score	66.3 (8.6)	66.4 (8.3)
ADCS-iADL score	47.8 (7.9)	47.8 (7.8)
MMSE score[e]	22.4 (3.8)	22.2 (3.9)
Screening MMSE category, n (%)[f]		
MCI (≥27)	146 (17.0)	137 (15.7)
Mild AD (20–26)	713 (82.9)	738 (84.3)
Moderate AD (<20)	1 (0.1)	0
Baseline MMSE category, n (%)[106-108,g]		
MCI (≥27)	142 (16.7)	124 (14.3)
Mild AD (20–26)	514 (60.5)	526 (60.6)
Moderate AD (10-19)	194 (22.8)	218 (25.1)
CDR-G score, n (%)		
0	2 (0.2)	4 (0.5)
0.5	514 (60.8)	532 (61.2)
1	304 (36.0)	308 (35.4)
2	25 (3.0)	25 (2.9)
Biomarker measures, mean (SD)		
Amyloid plaque level, Centiloid[h]	103.5 (34.5)	101.6 (34.5)
AD signature weighted neocortical flortaucipir SUVR[16,f,i]	1.34 (0.25)	1.35 (0.26)
Plasma P-tau217, pg/mL[j]	7.5 (18.5)	6.8 (15.4)

Footnotes: [a] Characteristics presented here were recorded at screening, which occurred prior to treatment initiation (baseline), which may result in some variation in numbers between screening and baseline. [b] Race data were self-reported by participants within fixed categories. [c] Ethnicity reporting was limited to participants in the US and Puerto Rico only; percentages were calculated using the number of participants with non-missing data as the denominator. [d] See Table 5 for further details on scales and their explanations. [e] Last non-missing MMSE score prior to or at the start of study treatment. [f] Based on screening data. [g] Baseline MMSE category figures do not match with the moderate numbers in the forest plots as the baseline characteristics values represent the ITT population rather than the analysed population. [h] Assessed with 18F-florbetapir or 18F-florbetaben PET. [i] Assessed with 18F-flortaucipir PET. Global tau uptake was measured using a composite neocortical SUVR with white matter signal reference.[109] [j] Plasma P-tau217 denotes plasma-measured phosphorylated tau at threonine 217, a blood biomarker specific to Alzheimer disease and associated with both amyloid and tau pathology.[110]

Abbreviations: ADAS-Cog$_{13}$: 13-Item Alzheimer's Disease Assessment Scale – Cognitive Subscale; ADCS-ADL, Alzheimer Disease Cooperative Study (Activities of Daily Living); ADCS-iADL, Alzheimer Disease Cooperative Study (Instrumental Activities of Daily Living); *APOE*, apolipoprotein E; CDR-G, Clinical Dementia Rating Global Score; CDR-SB, sum of boxes of the Clinical Dementia Rating Scale; iADRS, Integrated Alzheimer Disease Rating Scale; MMSE, Mini-Mental State Examination; P-tau217, phosphorylated tau 217; SUVR, standardised uptake value ratio.
Source: Sims *et al* (2023).[5]

B.2.4 *Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence*

The study populations and statistical analysis methods used in the TRAILBLAZER-ALZ 2 trial are summarised below. Participant flow (CONSORT) diagrams for the trial are presented in Appendix B.

B.2.4.1 Study populations

Study population definitions and the number of patients in the analysis sets of the trial are summarised in Table 8.

Table 8: Trial populations of TRAILBLAZER-ALZ 2

Analysis Population	n	Definition
Entered	1,800	All participants who sign informed consent
Randomised	1,736	All entered participants who are randomised to study treatment
Evaluable efficacy	[redacted] (iADRS) and (CDR-SB)	All randomised participants with a baseline and at least one post-baseline efficacy scale; this population are herein referred to as modified intent-to-treat (modified ITT) population
Safety	[redacted]	All randomised participants who are exposed to study drug. Participants will be summarised according to the treatment group to which they were randomised
Per-Protocol	[redacted] (iADRS) and (CDR-SB)	All subjects in the Evaluable Efficacy population who also: • signed the inform consent form • had an assessment of the primary endpoint at each scheduled visit completed • had no violations of inclusion/exclusion criteria • had no study dosing algorithm violation (such as if subjects randomised to treatment A were given treatment B or subjects randomised to treatment A never received the assigned study drug) • had no unqualified raters and no raters with substantial scoring errors for the primary measure • were not considered non-compliant with regard to study drug

Completers	[redacted] (iADRS) and (CDR-SB)	All randomised subjects who have disposition status of 'complete' or have at least 2 weeks exposure in visit interval 21

Source: Sims *et al.* (2023)[5]

B.2.4.2 Statistical methods

The statistical methods for the primary analysis of TRAILBLAZER-ALZ 2 are summarised in Table 9. Both natural cubic spline model (NCS) and mixed-effect model for repeated measures (MMRM) statistical analyses were conducted and, for the key endpoints, results from both analyses are presented throughout this submission. Further details on these analyses can be found in Table 9. Additionally, all secondary efficacy endpoints were controlled for multiplicity (gated) except for MMSE.

Table 9: Statistical methods for the primary analysis of TRAILBLAZER-ALZ 2

Hypothetical objective	The primary objective of this study was to test the hypothesis that IV infusion of donanemab slowed the cognitive and/or functional decline of AD as measured by iADRS score compared with placebo in the population of participants with low-medium tau pathology at baseline or the overall population. Thus, the null hypothesis tested in relation to the primary estimand was follows: H0: Least square (LS) mean change from baseline of iADRS score at 76 weeks from donanemab treated group was not different from the LS mean change from baseline of iADRS score at 76 weeks from placebo treated group, neither from participants with low-medium tau pathology at baseline, nor from overall population The null hypotheses corresponding to the secondary objectives were as follows: • LS mean change of CDR-SB score at 76 weeks from donanemab treated group was not different from the LS mean change of CDR-SB score at 76 weeks from placebo treated group, neither from participants with low-medium tau pathology at baseline, nor from overall population. • LS mean change of ADAS-Cog_{13} score at 76 weeks from donanemab treated group was not different from the LS mean change of ADAS-Cog_{13} score at 76 weeks from placebo treated group, neither from participants with low-medium tau pathology at baseline, nor from overall population. • LS mean change of iADL score at 76 weeks from donanemab treated group was not different from the LS mean change of iADL score at 76 weeks from placebo treated group, neither from participants with low-medium tau pathology at baseline, nor from overall population. • LS mean change of MMSE score at 76 weeks from donanemab treated group was not different from the LS mean change of MMSE score at 76 weeks from placebo treated group, neither from participants with low-medium tau pathology at baseline, nor from overall population. The null hypotheses for biomarker analyses were: • LS mean change of amyloid burden as measured by amyloid PET Centiloid values at 76 weeks from donanemab treated group was not different from that from placebo treated group. • LS mean change of brain tau deposition as measured by flortaucipir PET standard uptake value ratio (SUVR) values at 76 weeks from donanemab treated group was not different from that from placebo treated group • LS mean change of brain regional volumes as measured by volumetric

	MRI at 76 weeks from donanemab treated group was not different from that from placebo treated group
Statistical analysis	**Primary endpoint:** A NCS analysis (Donahue *et al*. 2023) with 2 degrees of freedom (NCS2) was be used to assess the difference between treatment groups in iADRS score at Week 76. For this NCS2 model applied to primary analysis, 3 knots over the observation time were placed: 2 at the boundaries (minimum and maximum observation time), and 1 internal knot at the median observation time. The baseline estimates were restricted to be the same for treatment and placebo groups. The model was estimated using a restricted maximum likelihood method. The iADRS score at baseline and at each of the scheduled post-baseline visits (according to SoA) was included in model as a dependent variable. Study visit was be treated as a continuous variable with values equal to weeks between baseline and postbaseline exam dates, and the NCS basis function was derived using these visits in weeks. The model included these fixed effects: NCS basis expansion terms (two terms), NCS basis expansion term-by-treatment interaction (two terms), baseline age, concomitant AChEI and/or memantine use at baseline (yes/no), and pooled investigator (as the study was conducted by multiple investigators at multiple sites internationally, data from all investigators was pooled). Baseline tau category was also be included as a covariate to the model applied to overall population. An unstructured variance-covariance structure matrix was used to within-subject variance-covariance errors. If the unstructured variance-covariance structure matrix resulted in a lack of convergence, the following structures were used in sequence: • Heterogeneous Toeplitz covariance structure • Heterogeneous autoregressive order 1 covariance structure • Heterogeneous compound symmetry covariance structure, and • Compound symmetry covariance structure Mean change from baseline values, and the comparisons between change from baseline values by treatment arms was estimated through the proper contrast set up. The primary time point for treatment comparison was at Week 76. The Kenward-Roger approximation was used to estimate the denominator degrees of freedom. Percent slowing comparing to placebo group was calculated as the LS estimates of differences in change from baseline between treatment groups at Week 76, divided by the LS estimates of mean change from baseline value from placebo group. A 95% confidence interval (CI) for this percent slowing was calculated based on a Delta method (Beyene *et al*. 2005).[111] For MMRM analysis, the change from baseline score on the iADRS at each scheduled postbaseline visit (according to the SoA) during the treatment period was included as the dependent variable. The model for the fixed effects included the following terms: baseline iADRS score, baseline score-by-visit interaction, pooled investigator, treatment, visit, treatment-by-visit interaction, concomitant AChEI and/or memantine use at baseline (yes/no), and age at baseline. Baseline tau category was also included as a fixed effect to the model applied to overall population. Visit was considered a categorical variable. An unstructured covariance matrix was used to model the within-subject variance-covariance errors. If the unstructured covariance structure matrix results in a lack of convergence, the following tests were used in sequence: • heterogeneous Toeplitz covariance structure • heterogeneous autoregressive covariance structure

	• heterogeneous compound symmetry covariance structure • compound symmetry covariance structure The Kenward-Roger approximation was used to estimate the denominator degrees of freedom. For MMRM, the primary time point for treatment comparison was at Week 76. The treatment group contrast in least-squares mean progression and its associated p-value and 95% CI was calculated for the treatment comparison of donanemab versus placebo using the MMRM model specified above. **Secondary endpoints:** Additional clinical and outcome measurements were analysed separately using NCS2 or MMRM analysis on both the overall population and the low-medium baseline tau subpopulation. Family wise type I error was controlled for the analyses included in the graphical testing scheme. MMRM analysis was applied as the main analytical approach for CDR-SB, with similar model details as described above. Other than CDR-SB, NCS2 analysis was applied to the rest of endpoint measurements as the main analytical approach on both the overall population and the low-medium baseline tau subpopulation separately. The models setup and adjusting covariates included to models was identical to what described above. In addition, CDR-SB was also tested using NCS2. **Biomarker secondary endpoints:** Participants' brain amyloid deposition was measured by amyloid PET imaging, either florbetapir F18, or florbetaben F18 at visits of screening, 24, 52 and 76 weeks. Both scan measurements were standardized to amyloid Centiloid following the specific formula for each tracer below, with details described in the Independent Review Charter (IRC) from PET imaging vendor. • ^{FBP} CL = 183.07 * ^{FBP} SUVr -177.26 • ^{FBB} CL = 156.06 * ^{FBB} SUVr – 148.13, Where ^{FBP} CL = florbetapir centiloid, ^{FBB} CL = florbetaben centiloid, ^{FBP} SUVr = florbetapir SUVr, and ^{FBB} SUVr = florbetaben SUVr. The change from baseline to the post-baseline visit of the amyloid imaging centiloid was evaluated using a MMRM model which includes the fixed, categorical effects of treatment, visit, and treatment-by-visit interaction, as well as continuous effects of baseline centiloid, baseline centiloid-by-visit interaction and age at baseline. Baseline tau category was also included as a fixed effect to the model applied to overall population. Visit will be considered a categorical variable with values equal to the visit numbers at which amyloid imaging is assessed. To assess the relationship of biomarker with cognition and function with treatment, Spearman's rank correlation coefficient was obtained on change from baseline at each follow up visit between centiloid change and change from baseline to Week 76 for iADRS, CDR-SB, $ADASCog_{13}$, ADCS-iADL, and MMSE. Correlation analyses was conducted by including patients from both treatment groups, as well as by treatment groups. Participant's brain tau deposition was measured using flortaucipir F18 PET scans. Global tau was measured as MUBADA (Muti-block Bayrecentric Discriminant Analysis) SUVr, an AD-signature region weighted SUVr and regional tau was measured at pre-specified region of interest including frontal, parietal, and posterior lateral temporal. All SUVr values were referenced to cerebellar crusteneous region. To evaluate donanemab treatment effect on brain tau accumulation, the change from baseline in tau imaging parameters (including global and regional tau SUVr) were assessed by an ANCOVA analysis in the Evaluable Efficacy Set (EES). The model was adjusted by baseline tau SUVr, and age at baseline.

	Baseline tau category was also included as a fixed effect to the model applied to overall population. To assess the relationship of biomarker with cognition and function with treatment, Spearman's rank correlation coefficient was obtained on change from baseline to Week 76 for the SUVr with change from baseline to Week 76 for iADRS, CDR-SB, ADAS-Cog_{13}, ADCS-iADL, and MMSE. Correlation analyses were conducted using only patients who have the clinical outcome and SUVr result at Week 76 and include patients from both treatment groups, as well as by treatment groups. Analyses of the following volumetric MRI (vMRI) parameters were conducted: • Bilateral hippocampal volume (mm3) • Atrophy of total whole brain volume (cm3) • Enlargement of Ventricular volume (cm3) To evaluate the changes in vMRI data after treatment, an MMRM model was used to compare change from baseline to 76 weeks in the EES dataset. The change from baseline to the endpoint visit was the dependent variable. The model included the fixed, categorical effect of treatment as well as the continuous effects of baseline vMRI value and age at baseline. Baseline tau category was also included as a fixed effect to the model applied to overall population. The null hypothesis was that the difference in LS means between donanemab and placebo equal zero.
Sample size, power calculation	Approximately 1,800 participants were randomised in the trial. It was anticipated that approximately two-thirds of participants would have low–medium tau and approximately one-third of participants would have high tau pathology. The powering and sample size determination of the trial was based on the low-medium tau pathology population. The assumptions for the power calculation were based on the results of the phase 2 trial data. The mean progression levels in the placebo and donanemab arms from the MMRM analysis on iADRS were −10.06 and −6.86 points (approximately 32% slowing) over 18 months, respectively, with a standard deviation of 11.06. The assumed discontinuation rate of the trial was 30%. Multiple longitudinal data sets were simulated, and the NCS model with 2 degrees of freedom was fit to each sample to determine the power. With a sample size of approximately 1,000 randomized participants in the low-medium tau pathology population, the NCS model with 2 degrees of freedom provides greater than 95% power to achieve statistical significance at a 2-sided 0.05 level for the treatment difference relative to placebo, as measured by iADRS at month 18. If both treatment arms are placebo-like with no efficacy, the 2-sided Type I error is 5%.
Data management, patient withdrawals	From the randomised population, the percentage of patients withdrawing from each treatment group was summarized. From the safety population, the percentage of patients withdrawing from each treatment group was compared between groups using Fishers exact test. Comparisons using Fisher's exact test were done for the overall percentage of patients who withdraw and also for each specific reason for withdrawal.

Abbreviations: AChEI: acetylcholinesterase inhibitors; ADAS-Cog_{13}: Alzheimer Disease Assessment Scale (Cognitive subscale); CDR-SB: sum of boxes of the Clinical Dementia Rating Scale; CI: confidence interval; EES: Evaluable Efficacy Set; iADRS: Integrated Alzheimer Disease Rating Scale; CL: Centiloid; LS: least square; MMRM: mixed-effect model for repeated measures; MMSE: Mini-Mental State Examination; NCS: natural cubic spline model; SoA: Schedule of Activities; SUVr: standard uptake value ratio; vMRI: volumetric magnetic resonance imaging.
Source: Sims *et al* (2023).[5]

B.2.5 *Critical appraisal of the relevant clinical effectiveness evidence*

A quality assessment of the TRAILBLAZER-ALZ 2 trial was conducted using the Cochrane risk of bias assessment tool version 2.0, which covers all criteria required by NICE and recommended by IQWiG to establish whether studies are suitable to inform decision making.[112-114] The trials identified in the SLR were assessed using the same tool.

A summary of the quality assessment is presented in Table 10; the full version of this quality assessment and the quality assessments for the remaining trials identified in the SLR are presented in Appendix B.

Table 10: Assessment of quality and risk of bias in the TRAILBLAZER-ALZ 2 trial

Criteria	Risk of bias in TRAILBLAZER-ALZ 2
Bias arising from the randomisation process	Low
Bias due to deviations from intended interventions	Some concerns in the potential for study unblinding due to the occurrence of ARIA events
Bias due to missing outcome data	Low
Bias in measurement of the outcome	Low
Bias in selection of the reported result	Low
Overall bias judgement	Some concerns

Abbreviations: ARIA: amyloid-related imaging abnormality.

B.2.6 *Clinical effectiveness results of the relevant studies*

B.2.6.1 Clinical assessment endpoints

iADRS: primary endpoint

iADRS assesses the impact of cognitive loss on the ability to conduct everyday activities and provides a measure of global AD severity as a single summary score. The composite score comprises two underlying domains: cognitive ability and functional ability.

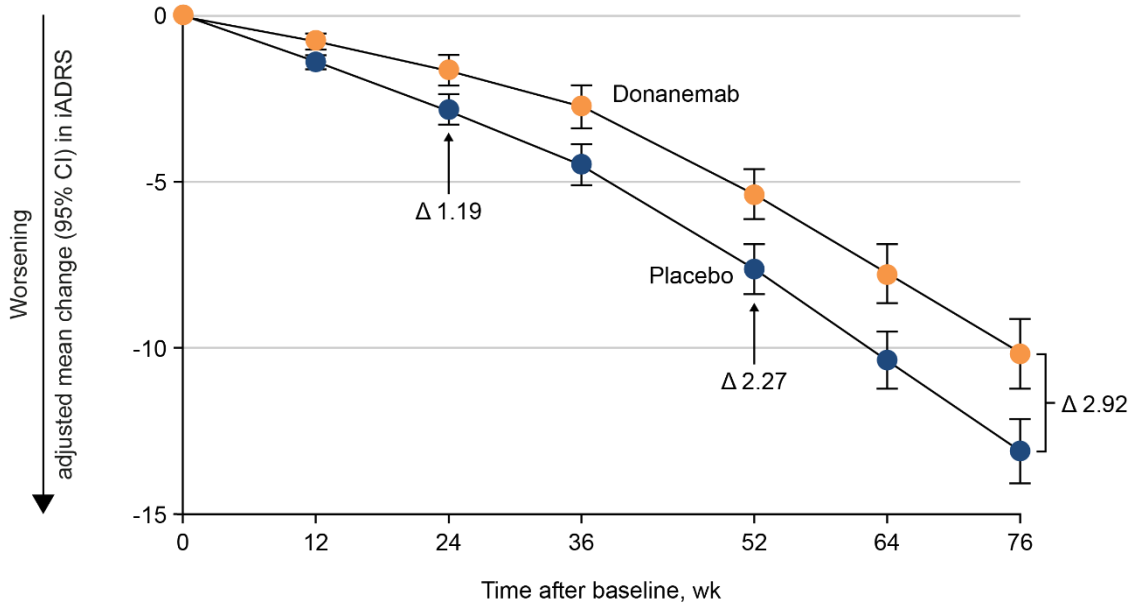
iADRS captures clinical progression from MCI due to AD through moderate dementia due to AD, and treatment effects have been demonstrated across MCI due to AD and mild dementia due to AD.[4, 115, 116]

The actual scales administered to participants in the trial were the ADAS-Cog_{13} and the ADCS-ADL.

In the overall population, the primary trial endpoint was met and donanemab significantly slowed disease progression by 22.3% (95% CI, 11.38% to 33.15%) as measured by the iADRS score (Figure 6). Least-squares mean (LSM) change from baseline to 76 weeks in iADRS was −10.19

(95% CI,−11.22 to −9.16) in the donanemab group and −13.11 (95% CI, −14.10 to −12.13) in the placebo group. This represents an improvement in iADRS score of 2.92 (95% CI, 1.51 to 4.33, p<0.001). The treatment effect of donanemab widened over time, with a LSM difference versus placebo of –1.19, –2.27, and –2.92 at Weeks 24, 52, and 76, respectively.

Figure 6: iADRS from baseline to 76 weeks in the overall population (NCS2)



No. of participants							
Placebo	824	805	767	738	693	651	653
Donanemab	775	752	712	665	636	579	583

Abbreviations: CI: confidence interval; iADRS: integrated Alzheimer disease rating scale; NCS2: natural cubic spline with 2 degrees of freedom; No.: number; wk: week.
Source: Sims *et al*. (2023).[5]

CDR-SB: key secondary endpoint

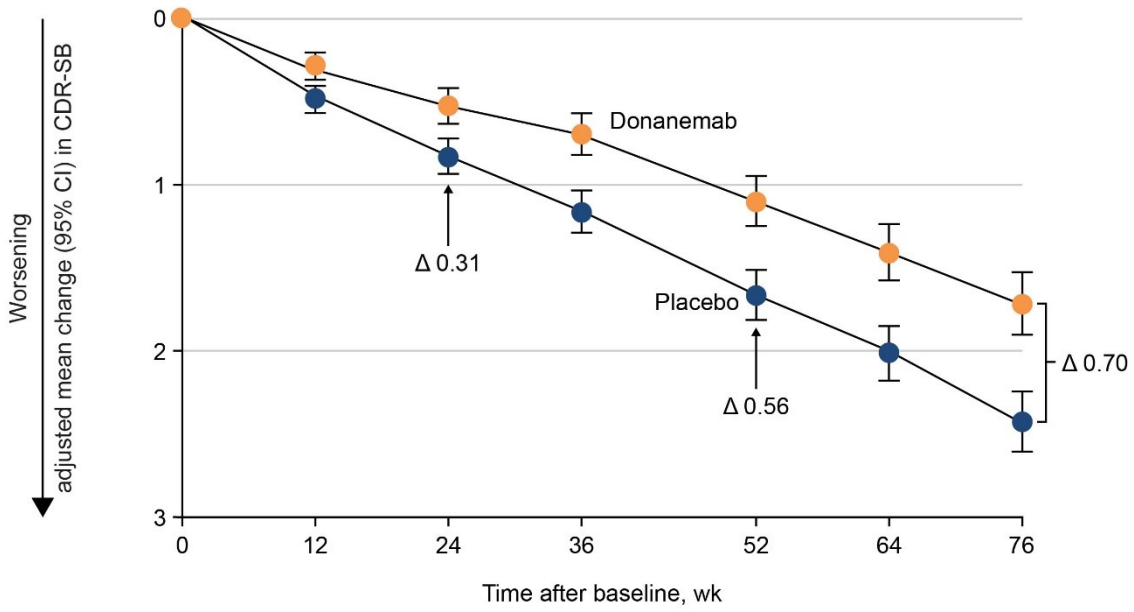
CDR is a global assessment tool that can be used to effectively evaluate both cognition and function.[117, 118] The tool covers 6 categories or "boxes": memory, orientation, judgement and problem solving, community affairs, home and hobbies, and personal care.

The CDR global ratings, calculated using an algorithm, range from 0 (no dementia) to 3 (severe dementia) while CDR-SB scores, calculated by adding the box scores, range from 0 to 18 (with higher scores indicative of more impairment). Scoring is determined by a clinician through a semi-structured and in-depth interview with both the affected individual and their study partner.

This scale demonstrates acceptable psychometric characteristics and has been shown to be sensitive enough to detect disease progression, even in populations with less advanced clinical disease.[119-122] CDR is also a commonly used endpoint in clinical trials.[123, 124]

Consistent with the primary efficacy endpoint results, donanemab was associated with a significant and clinically meaningful slowing of disease progression compared with placebo as measured by the CDR-SB score in the overall population.

Figure 7: CDR-SB from baseline to 76 weeks in the overall population (MMRM)



No. of participants							
Placebo	838	825	784	752	713	678	672
Donanemab	794	774	731	682	650	603	598

Abbreviations: CI: confidence interval; CDR-SB: Sum of Boxes of the Clinical Dementia Rating Scale; No.: number; wk: week.
Source: Sims *et al*. (2023).[5]

Donanemab was associated with 28.9% (95% CI, 18.26% to 39.53%) slowing of clinical progression compared to placebo on the CDR-SB scale (Figure 7), in the overall population. At 76 weeks, there was a significant difference between the donanemab and placebo arms with a LSM difference of −0.70 (95% CI, −0.95 to −0.45). A significant separation from placebo occurred as early as Week 12 and the treatment effect continued to increase over time to Week 76 (Figure 7), with a LSM difference compared with placebo of –0.31, –0.56, and –0.70 at Weeks 24, 52, and 76, respectively. Evidence suggests that a change versus placebo in the CDR-SB of –0.5 is an indication of clinical significance.[125, 126]

In addition, exploratory post-hoc analyses of the TRAILBLAZER-ALZ 2 trial data by Atri *et al*. (2023), demonstrated that donanemab was statistically significant versus placebo on all six CDR-SB domains.[127] Therefore, donanemab treatment slowed clinical progression in all cognitive and functional domains captured (memory, orientation, judgment/problem solving, community affairs, home/hobbies, and personal care) and a clinically relevant treatment effect is clearly demonstrated in patients with MCI due to AD and mild AD dementia.

Other secondary endpoints

Donanemab slowed cognitive and functional decline across all key secondary end points. All secondary endpoints were controlled for multiplicity (gated), except for the MMSE endpoint (due to necessary prioritisation of endpoints). Results across key functional and cognitive scales for the overall population are summarised in Table 11 and show that donanemab was consistently

associated with improvements across all cognitive and functional endpoints tested, regardless of statistical model.

In both the NCS2 and MMRM statistical analyses, the LSM change from baseline across all key outcomes was associated with a statistically significant improved difference between the donanemab-treated and placebo groups. The percentage of slowing of clinical progression was calculated by dividing the LSM change from baseline treatment differences at 76 weeks by the LSM change from baseline with placebo at 76 weeks and multiplying by 100.

The NCS2 differences between treatment groups in the LSM change from baseline at 76 weeks for the functional ADCS-iADL scale demonstrated a 27.8% (95% CI, 13.48% to 42.13%) slowing of clinical progression compared to placebo. Similarly, treatment with donanemab was associated with 19.5% (95% CI, 8.23% to 30.83%) slowing of clinical progression compared to placebo on the cognitive ADAS-Cog_{13} scale, and a 16.1% (95% CI, 3.49 to 28.67) slowing of clinical progression on the MMSE. Overall, clinical outcome results were consistent across all key outcomes.

Table 11: Clinical outcomes from baseline to 76 weeks in the overall population

Outcome[a]	Statistical method	Donanemab			Placebo			LSM difference vs placebo (95% CI)	p value vs placebo	Slowing of clinical progression, % (95% CI)[b]
		Mean (SD)		LSM change (95% CI)	Mean (SD)		LSM change (95% CI)			
		Baseline	76 Weeks		Baseline	76 Weeks				
iADRS		n=775	n=583		n=824	n=653				
	NCS2[c]	104.55 (13.90)	96.98 (20.87)	−10.19 (−11.22, −9.16)	103.82 (13.88)	93.82 (20.38)	−13.11 (−14.10, −12.13)	2.92 (1.51, 4.33)	<0.001	22.3 (11.38, 33.15)
	MMRM[d]	104.55 (13.90)	96.98 (20.87)	−10.19 (−11.27, −9.11)	103.82 (13.88)	93.82 (20.38)	−13.22 (−14.27, −12.18)	3.03 (1.60, 4.47)	<0.001	22.9 (11.96, 33.92)
CDR-SB		n=794	n=598		n=838	n=672				
	NCS2	3.92 (2.06)	5.25 (3.21)	1.66 (1.48, 1.83)	3.89 (2.03)	5.80 (3.22)	2.33 (2.16, 2.50)	−0.67 (−0.92, −0.43)	<0.001	28.9 (18.26, 39.53)
	MMRM[c,d]	3.92 (2.06)	5.25 (3.21)	1.72 (1.53, 1.91)	3.89 (2.03)	5.80 (3.22)	2.42 (2.24, 2.60)	−0.70 (−0.95, −0.45)	<0.001	28.9 (18.41, 39.44)
ADCS-iADL		n=780	n=591		n=826	n=661				
	NCS2[c]	47.96 (7.85)	44.53 (11.06)	−4.42 (−5.05, −3.80)	47.98 (7.70)	43.30 (10.61)	−6.13 (−6.72, −5.53)	1.70 (0.84, 2.57)	<0.001	27.8 (13.48, 42.13)
	MMRM[d]	47.96 (7.85)	44.53 (11.06)	−4.57 (−5.24, −3.90)	47.98 (7.70)	43.30 (10.61)	−6.32 (−6.97, −5.67)	1.75 (0.86, 2.64)	<0.001	27.7 (13.37, 42.00)
ADAS-Cog$_{13}$		n=797	n=607		n=841	n=677				
	NCS2[c]	28.53 (8.78)	32.72 (12.44)	5.46 (4.91, 6.01)	29.16 (8.85)	34.53 (12.00)	6.79 (6.26, 7.32)	−1.33 (−2.09, −0.57)	<0.001	19.5 (8.23, 30.83)

	MMRM[d]	28.53 (8.78)	32.72 (12.44)	5.70 (5.10, 6.30)	29.16 (8.85)	34.53 (12.00)	7.05 (6.47, 7.63)	−1.35 (−2.14, −0.57)	<0.001	19.2 (7.99, 30.38)
MMSE		n=796	n=600		n=841	n=679				
	NCS2	22.52 (3.84)	20.71 (5.52)	−2.47 (−2.73, −2.20)	22.20 (3.90)	19.79 (5.51)	−2.94 (−3.20, −2.69)	0.47 (0.10, 0.84)	0.01	16.1 (3.49, 28.67)
	MMRM[d]	22.52 (3.84)	20.71 (5.52)	−2.75 (−3.05, −2.44)	22.20 (3.90)	19.79 (5.51)	−3.22 (−3.51, −2.93)	0.48 (0.08, 0.87)	0.02	14.8 (2.46, 27.06)

Footnotes: [a]Clinical outcomes were scored as follows: ADAS-Cog$_{13}$ scores range from 0 to 85, with higher scores indicating greater overall cognition deficit; ADCS-iADL range from 0 to 59, with lower scores indicating greater impairment in daily function; CDR-SB range from 0 to 18, with higher scores indicating greater clinical impairment; iADRS range from 0 to 144, with lower scores indicating greater impairment; and MMSE range from 0 to 30, with lower scores indicating greater level of impairment.
[b]The percentage of slowing of clinical progression was calculated by dividing the LSM change from baseline treatment differences at 76 weeks by the LSM change from baseline with placebo at 76 weeks and multiplying by 100. The CI was estimated using the Delta method. [c]Gated outcome, also indicated via grey shaded cells. [d]For MMRM analyses, 95%CIs for LSM changes were calculated with the normal approximation method.
Abbreviations: ADAS-Cog$_{13}$ 13-Item Alzheimer's Disease Assessment Scale – Cognitive Subscale; ADCS-iADL: Alzheimer Disease Cooperative Study–Instrumental Activities of Daily Living; CDR-SB: sum of boxes of the Clinical Dementia Rating Scale; CI: confidence interval; iADRS: Integrated Alzheimer Disease Rating Scale; LSM: least-squares mean; MMRM: mixed models for repeated measures; MMSE: Mini-Mental State Examination; NCS2: natural cubic spline with 2 degrees of freedom.
Source: Sims *et al*. (2023).[5]

B.2.6.2 Time-based analyses

Time-based analyses are valuable when evaluating clinical data in Alzheimer's disease, allowing interpretation of whether an intervention can slow disease progression and therefore delay transition into a subsequent stage of the disease, where QoL is worse. These analyses are especially useful for patients, they are an intuitive metric and will be readily understood as translating to preserving independence, longer participation in daily activities, and retaining relationships and sense of self.

At 76 weeks, in the overall population, treatment with donanemab delayed disease progression by 1.38 months (95% CI, 0.46, 2.3) on the iADRS scale and 5.44 months (95% CI, 3.90, 6.98) on the CDR-SB scale (Table 12). It is important to note that these results are in the context of the 18-month trial period, and time saved would be expected to increase when projected over subsequent years.

Table 12: Time-based analyses in the overall population[a]

	Donanemab	Placebo
Delayed disease progression at 76 weeks as measured by iADRS[b]		
Months saved versus placebo (95% CI)	1.38[c] (0.46, 2.3)	-
Percent time savings (95% CI)	7.89 (2.64, 13.13)	-
P value versus placebo	0.004	-
Delayed disease progression at 76 weeks as measured by CDR-SB[b,d]		
Months saved versus placebo (95% CI)	5.44 (3.90, 6.98)	-
Percent time savings (95% CI)	31.0 (22.21, 39.79)	-
P value versus placebo	<0.001	-
No progression at 52 weeks as measured by CDR-SB[b,e]		
Estimated percent of no progression (95% CI)	36% (33, 40)	23% (20, 26)
P value versus placebo	<0.001	-

Footnotes: [a] The overall population was not prespecified as gated in the statistical analysis plan. [b] iADRS scores range from 0 to 144, with lower scores indicating greater impairment, and CDR-SB scores range from 0 to 18, with higher scores indicating greater clinical impairment. [c] The model assumed proportional time slowing. Results from the test of non-proportional time slowing at 76 weeks was 2.47 months saved (95% CI, 1.12, 3.82), but the proportional time slowing assumption was marginally met for the iADRS (p = 0.052 from a likelihood ratio test). [d] The model assumed proportional time slowing. [e] No progression was defined as a CDR-SB score change from baseline of less than or equal to 0.
Abbreviations: CDR-SB: Clinical Dementia Rating Scale – Sum of Boxes; iADRS: Integrated Alzheimer's Disease Rating Scale.
Source: Sims *et al.* (2023).[5]

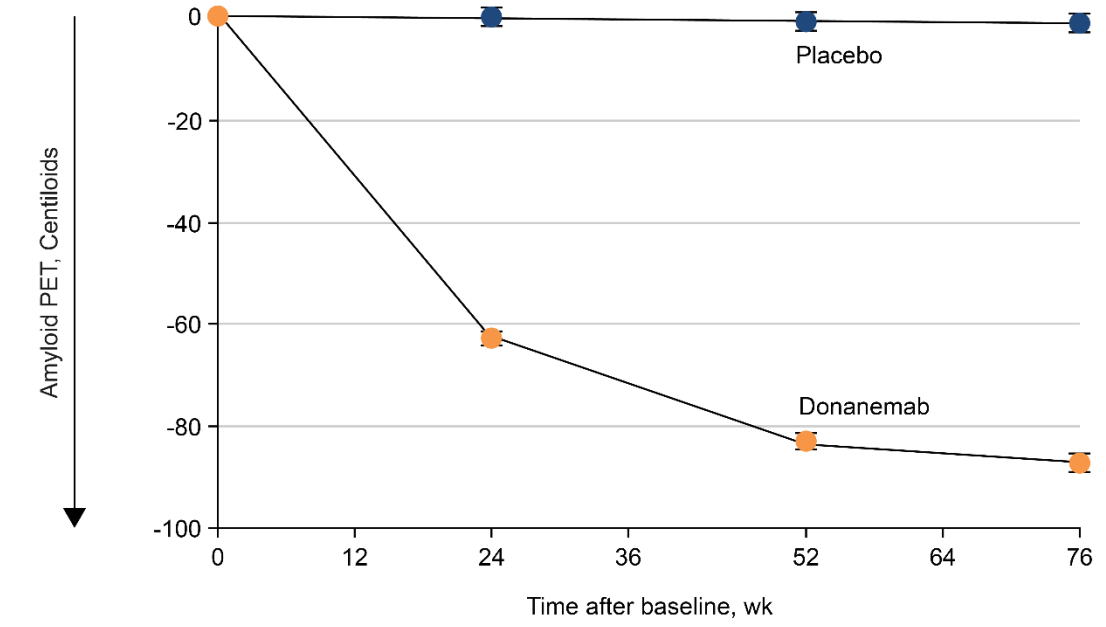
B.2.6.3 Biomarker endpoints

Amyloid PET

Amyloid PET scans can be used to demonstrate clearance of amyloid plaques (a defining feature of AD pathology). Donanemab targets a form of Aβ present only in amyloid plaques and facilitates their removal from the brain via microglial-mediated phagocytosis,[2-5] so amyloid clearance is of particular importance. Within the trial, amyloid clearance was defined as <24.1 Centiloids measured by amyloid PET and was assessed at 24 weeks and 76 weeks within the trial.[4, 128]

Treatment with donanemab was associated with a decrease in overall brain amyloid plaque level from baseline to 76 weeks. In the overall population, brain amyloid plaque level in patients treated with donanemab decreased by 87.0 Centiloids (95% CI, −88.90 to −85.17) compared to 0.67 Centiloids (95% CI, −2.45 to 1.11) in the placebo group (Figure 8). As described in Section B.1.2, donanemab is directed at an N3pG Aβ epitope, present only on established amyloid plaques and facilitates their removal through microglial-mediated clearance. The reduction in brain amyloid plaque level described is therefore an expected outcome of donanemab treatment.

Figure 8: Adjusted mean change (95%) in amyloid PET

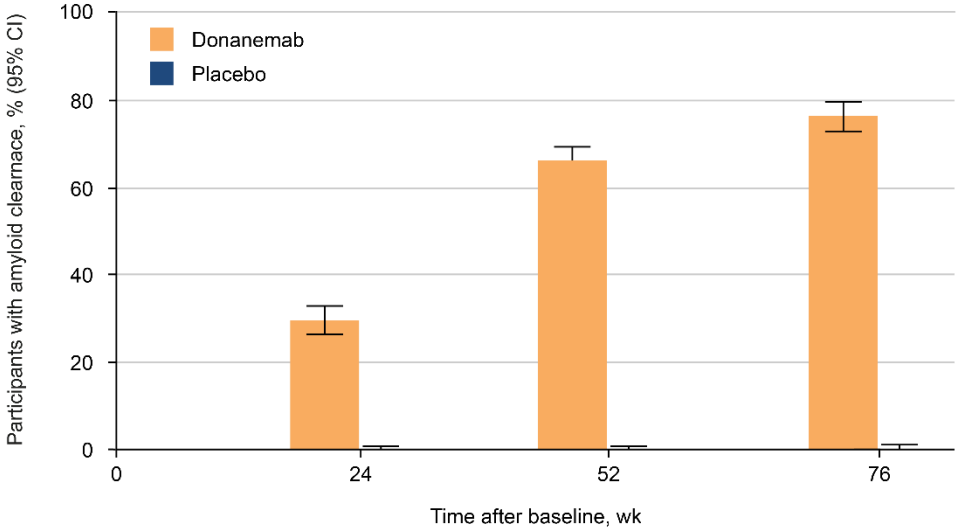


No. of participants				
Placebo	812	805	729	690
Donanemab	765	760	670	614

Abbreviations: CI: confidence interval; PET: positron emission tomography; wk: week.
Source: Sims *et al*. (2023).[5]

At 76 weeks in the overall population, 76.4% (95% CI, 72.87% to 79.57%) of patients treated with donanemab reached amyloid clearance compared to 0.3% (95% CI, 0.08% to 1.05%) of patients treated with placebo (Figure 9).

Figure 9: Participants with amyloid clearance (<24.1 Centiloids)



No. of participants			
Placebo	805	730	690
Donanemab	761	670	614

Abbreviations: CI: confidence interval; wk: week.
Source: Sims *et al*. (2023).[5]

Tau biomarkers

Tau lies downstream of amyloid in AD pathogenesis, with amyloid hypothesised to trigger the conversion of tau from a normal to a toxic state.[129] Tau PET scans were therefore conducted within the trial, monitoring frontal tau standardised uptake value (SUVR; cerebellar grey reference), to analyse any potential downstream effects of treatment with donanemab. Evaluation of the LSM change from baseline to 76 weeks in frontal tau SUVR did not show a significant difference in the overall or in the low-medium tau population. The difference in LSM change in tau SUVR from placebo in the frontal lobe at 76 weeks was −0.0041 (95% CI, −0.01 to 0.01; p=0.45) in the overall population. Although the lack of response in frontal tau PET is inconsistent with the TRAILBLAZER-ALZ phase 2 results (which demonstrated a greater reduction in tau accumulation in frontal and temporal lobe regions in the donanemab group than in the placebo group),[4] there are likely multiple contributory factors to this.[130]

A significant response to donanemab treatment in plasma P-tau217 was however observed.[5] In donanemab-treated participants, a [redacted]% decrease from baseline to Week 76 was observed in plasma P-tau217 (a gated exploratory endpoint) compared with a [redacted]% increase in the placebo group (p<0.0001). The difference in LSM change versus placebo was –0.22 (95 % CI –0.24, –0.20). Statistical separation between the two groups was observed as early as 12 weeks after the start of treatment, demonstrating that donanemab is able to reverse the increases in tau typically observed in AD. This could reflect a combination of less tau spread in the brain and less neuronal stress or damage, which could account for the tau leakage into the periphery that is observed in the absence of treatment.

vMRI

At 76 weeks, vMRI (a non-gated secondary outcome) showed a greater decrease in whole brain volume (p<0.0001 at 76 weeks), a lesser decrease in the hippocampal volume (p<0.0001 at 76 weeks), and a greater increase in ventricular volume (p<0.0001 at 76 weeks) in the donanemab group than in the placebo group. These paradoxical findings are aligned with previous clinical trials of disease-modifying AD therapies and are hypothesised to be a form of pseudoatrophy, rather than accelerated neurodegeneration.[131, 132]

The reasons for this paradoxical finding are not completely clear but may be related to the biphasic trajectory of brain structural changes observed in AD, where cortical thickening in earlier disease stages is followed by cortical thinning and increases in cortical diffusivity.[133, 134] It has been proposed that amyloid-related inflammatory processes cause cortical thickening and that treatments that directly or indirectly decrease brain inflammation could, therefore, result in a reduction in brain volume compared with placebo.[132]

This is further supported by non-gated exploratory endpoints NfL and GFAP data. NfL and GFAP are intermediate filament proteins which are important structural components of the cytoskeleton of neurons and astrocytes, and which have a role in neurodegenerative and inflammatory changes in AD.[135, 136] Firstly, there was no clear pattern in NfL levels. Donanemab was associated with a significant increase in plasma NfL compared with placebo at Weeks 12 (p<0.01) and 24 (p≤0.001) but no significant difference between treatment groups was observed at Weeks 52 and 76. Compared with placebo, donanemab significantly reduced plasma GFAP levels, starting as early as week 12. At week 76, donanemab treatment was associated with a 19.2% reduction in plasma GFAP compared with an 11.4% increase in those receiving placebo.[137] These findings support that the global atrophy seen on vMRI is unlikely to represent accelerated neurodegeneration with donanemab.

B.2.6.4 HRQoL endpoints

QoL-AD

Utility measures as provided by standard questionnaires such as EQ-5D may have some limitations in reflecting the full impact of progression in the QoL of patients. A subset of the total TB2 sample was included in an addendum to the phase 3 study and HRQoL data were collected using the Quality of Life in Alzheimer's Disease (QoL-AD) questionnaire.

The QoL-AD is a 13-item disease-specific questionnaire for measuring QoL in AD.[138] It uses a scale of 1–4 (poor, fair, good, or excellent) to rate a variety of life domains, including the patient's physical health, mood, relationships, activities, and ability to complete tasks.[139] The questionnaire can either be completed by the patient themselves (patient-assessed) or by a carer or family member (proxy-assessed). Patient and caregiver reports of QoL differ from each other over the course of the disease.[138, 139]

QoL-AD was collected in a subset of patients and their caregivers. The changes from baseline in patient-assessed (n=[redacted] in the placebo arm, and n=[redacted] in the donanemab arm) and proxy-assessed (n=[redacted] in the placebo arm, n=[redacted] in the donanemab arm) QoL-AD score in the evaluable efficacy set are summarised below.

Patient-assessed QoL-AD

At 76 weeks, the LSM change from baseline subject-measured QoL-AD score was [redacted] in the donanemab group, compared with [redacted] in the placebo group. The difference in LSM change in

subject-measured QoL-AD score at 76 weeks was [redacted](95% CI, [redacted]; p=[redacted]), which was not statistically significant.

Proxy-assessed QoL-AD

At 76 weeks, the LSM change from baseline subject-measured QoL-AD score was [redacted] in the donanemab group, compared with [redacted] in the placebo group. The difference in LSM change in subject-measured QoL-AD score at 76 weeks was [redacted] (95% CI, [redacted]; p=[redacted]), which was not statistically significant.

B.2.6.5 Analysis of clinical effectiveness results for the economic analysis

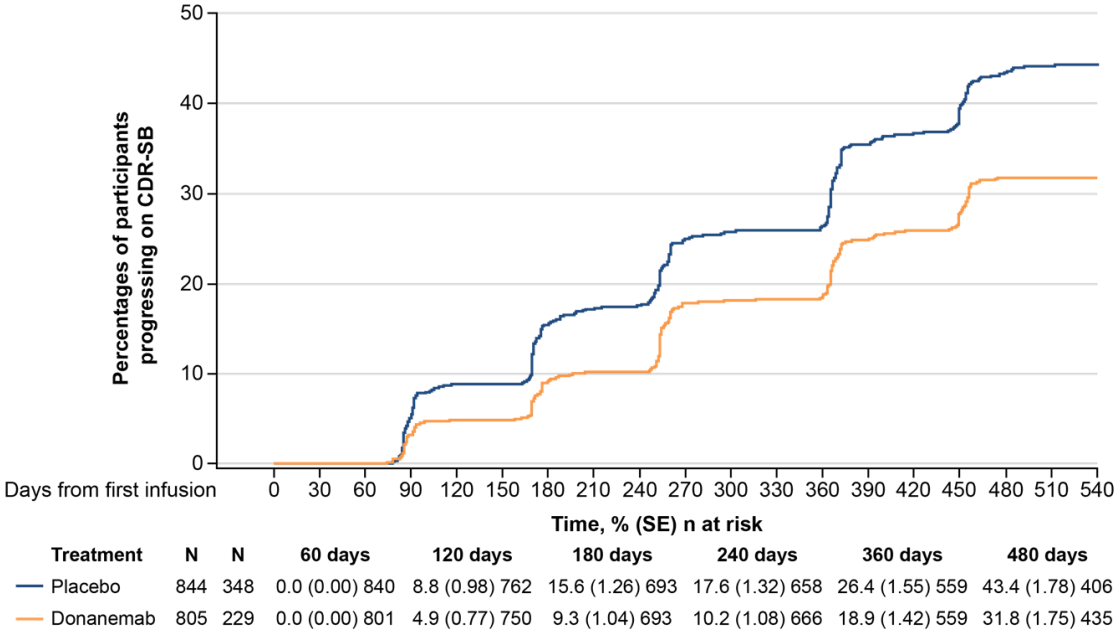
The hazard ratio (HR) of progressing to clinical worsening between donanemab and BSC was estimated using a Cox proportional hazard (CPH) model, with a clinical worsening defined as:

- A 1-point or 0.5-point increase from baseline in the CDR-SB in participants with MCI or mild dementia due to AD, respectively (prespecified; non-gated)[140]

The definitions of MCI and Mild were based on the MMSE value at screening. For each of the clinical endpoints, a clinical worsening event was defined as meeting the clinical worsening criteria at two consecutive visits during the double blinded phase. A CPH model was fitted to the modified-ITT data from the TRAILBLAZER-ALZ 2 trial to evaluate the hazards of progressing to the defined clinical worsening events by treatment arms. The analysis was modelled as time to first occurrence of the event, and adjusted for baseline age, score, and concomitant AChEI and/or memantine use at baseline (yes/no). The model was further stratified by pooled investigator sites, and the baseline tau category.

A lower risk of progression with substantial decline was observed for donanemab-treated participants compared with placebo-treated participants in the pre-specified non-gated analysis of CDR-SB. Analysis using the CPH model demonstrated that donanemab was associated with a 38% lower risk of progression as measured by the CDR-SB (HR 0.62 [95% CI 0.52 to 0.75]; nominal p<0.001) (Figure 10). These results are also consistent with the pre-specified gated analysis of time to disease progression using the CDR-GS (HR 0.63 [95% CI: 0.51 to 0.77]; p<0.001) as well as with a non-pre-specified analyses on time to deterioration to a more severe health state (as defined for the probability transitions) using CDR-SB (HR 0.61 [95% CI 0.50 to 0.74]; p<0.001) from TRAILBLAZER-ALZ 2.

Figure 10: Hazard ratio of progression: CDR-SB



Abbreviations: CDR-SB: clinical dementia rating scale–sum of boxes; CI: confidence interval; HR: hazard ratio; SE: standard error.
Source: Sims *et al*. (2023).[5]

Differences in treatment effect were explored across the different AD severities. The CPH model described above defined clinical progression based on AD severity at screening (i.e. including only patients with MCI due to AD and patients with mild AD). The interaction between AD severity (at screening) and the study treatment was tested and was not statistically significant. However, a substantial number of patients were considered to be in the moderate AD category at baseline, as 389 (23.7%) of those patients who contributed to the analyses had a baseline MMSE score between 10 and 19. As such, a similar CPH model of clinical progression, with AD severity defined according to the MMSE category at baseline, was re-run. As in the first model, the interaction between the AD severity (at baseline) was not significant. As there was no evidence of a difference in treatment effect across the different AD severities, the same overall treatment effect estimate was used in the economic model for all severities, including for moderate AD.

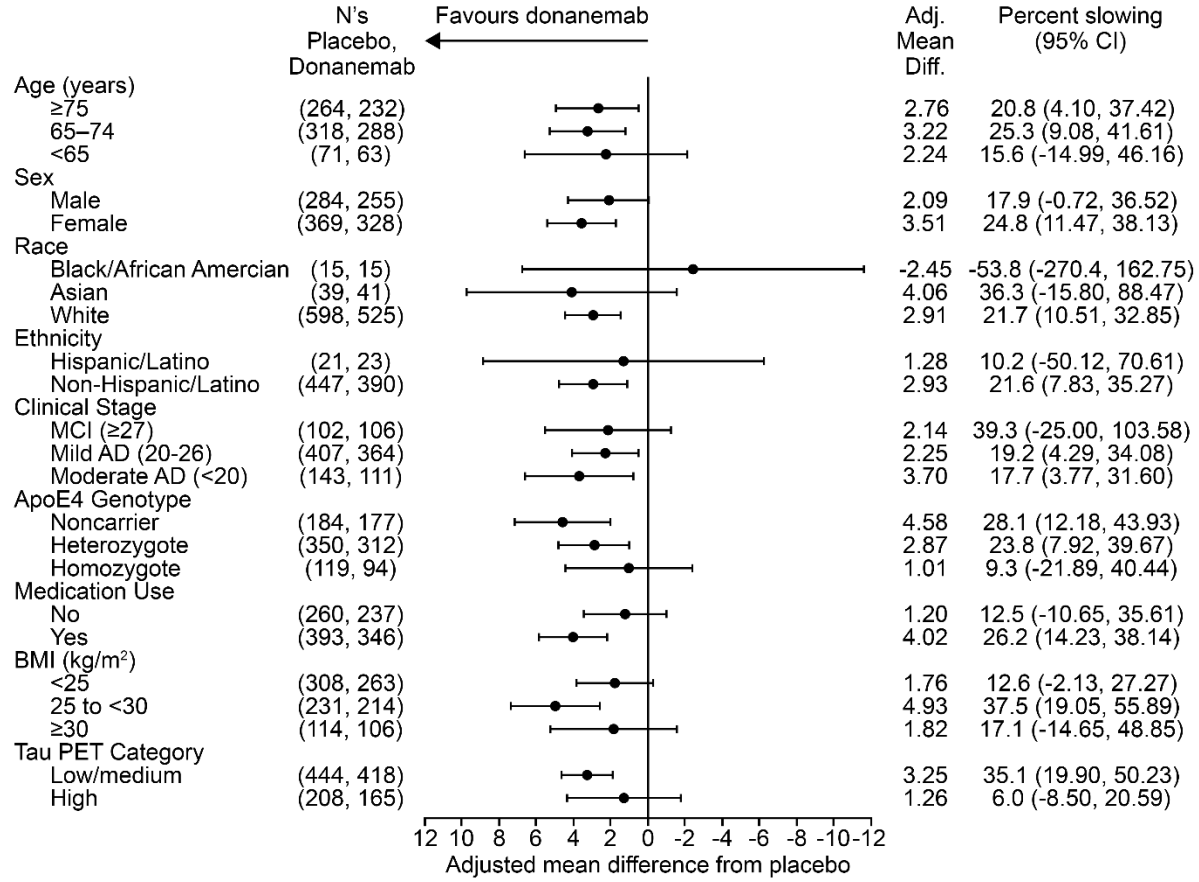
B.2.7 *Subgroup analysis*

Primary analyses were also conducted in a subgroup of participants with low/medium tau pathology (determined using flortaucipir F18 PET imaging), the population that was studied in the phase 2 trial. A summary of these results can be found in Appendix C.

Further subgroup analyses were conducted for the adjusted mean difference at 76 weeks in the donanemab group compared with the placebo group for the iADRS and the CDR-SB. Forest plots for the iADRS and CDR-SB subgroup analyses in the overall population are presented in Figure 11 and Figure 12, respectively.

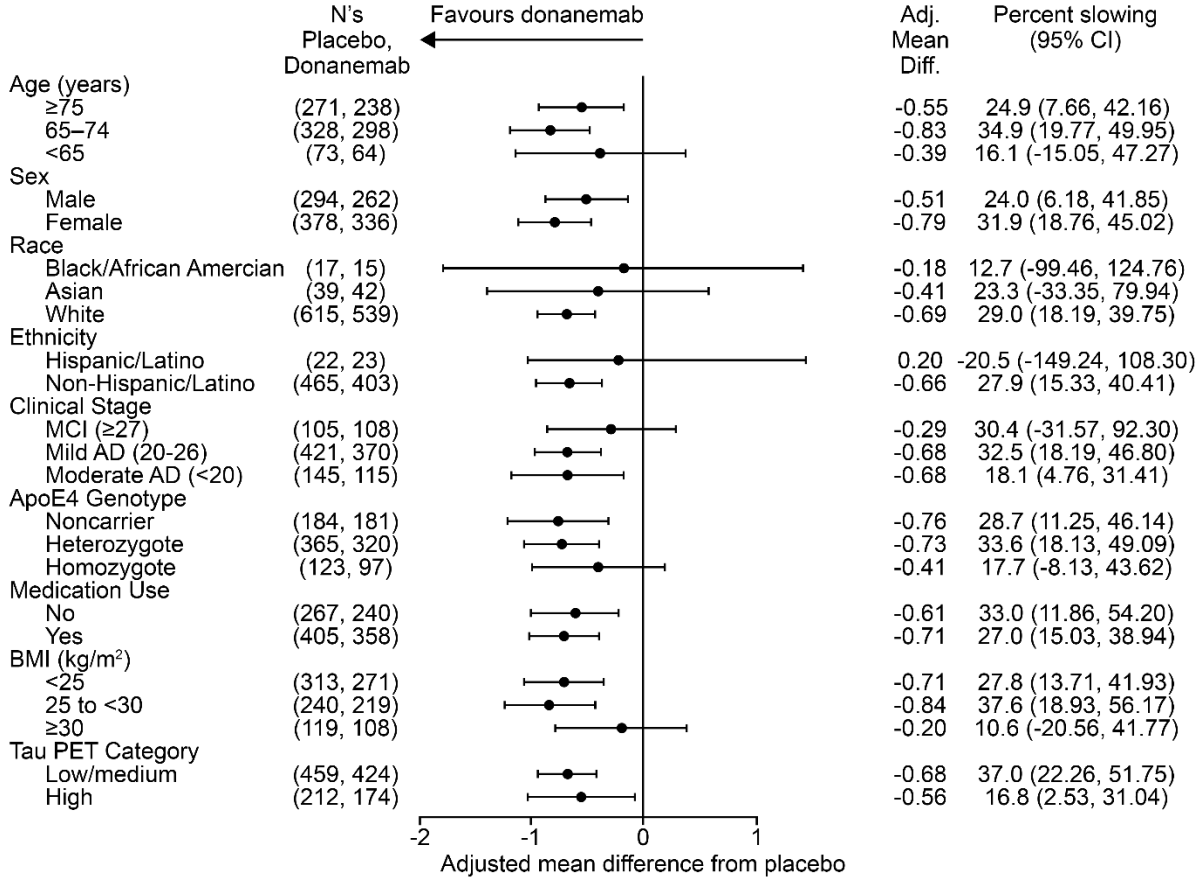
In cases where the point estimates cross the line of indifference, subgroups have very small sample sizes leading to additional uncertainty within these results, as demonstrated by the large confidence intervals.

Figure 11: Forest plot of baseline characteristic subgroup analyses for the iADRS in the overall population



Abbreviations: Adj. Mean Diff.: adjusted mean difference; AD: Alzheimer's disease; ApoE: apolipoprotein E; BMI: body mass index; CDR-SB: clinical dementia rating scale–sum of boxes; CI: confidence interval; iADRS: integrated Alzheimer's disease rating scale; MCI: mild cognitive impairment; N: number of participants; PET: positron emission tomography.
Source: Sims *et al.* (2023)[5]

Figure 12: Forest plot of baseline characteristic subgroup analyses for the CDR-SB in the overall population



Abbreviations: Adj. Mean Diff.: adjusted mean difference; AD: Alzheimer's disease; ApoE: apolipoprotein E; BMI: body mass index; CDR-SB: clinical dementia rating scale–sum of boxes; CI: confidence interval; iADRS: integrated Alzheimer's disease rating scale; MCI: mild cognitive impairment; N: number of participants; PET: positron emission tomography.
Source: Sims *et al.* (2023)[5]

B.2.8 *Meta-analysis*

No meta-analyses were conducted.

B.2.9 *Indirect and mixed treatment comparisons*

No indirect or mixed treatment comparisons were conducted.

B.2.10 *Adverse reactions*

A summary of adverse events from the TRAILBLAZER-ALZ 2 trial, and from the integrated safety dataset of data from the TRAILBLAZER-ALZ, TRAILBLAZER-ALZ 2 (including the placebo-controlled, long-term extension [LTE] periods and the safety addendum), TRAILBLAZER-ALZ LTE (Part B), and TRAILBLAZER-ALZ 4 (donanemab cohort) trials is presented in Table 13. The integrated safety dataset included all participants on donanemab or placebo who received at least 1 dose of study treatment in those trials, measured from the first dose of donanemab to end

of treatment period +57 days. In general, results from the integrated dataset were consistent with TRAILBLAZER-ALZ 2 safety data.

In the TRAILBLAZER-ALZ 2 trial, the incidence of serious adverse events was 17.4% in the donanemab group and 15.8% in the placebo group. Treatment-emergent AEs (TEAEs) were reported by 89.0% of patients in the donanemab group and 82.2% of the placebo group. In the integrated dataset, the incidence of serious adverse events was [redacted]%, and TEAEs were reported by [redacted]% of patients. TEAEs reported at a ≥5% incidence from both the phase 3 trial and integrated dataset are summarised in Table 14.

Table 13: Summary of adverse events by treatment group

Event, No. (%)	Donanemab All, Integrated Dataset (n=2,727)	Donanemab TB2 (n=853)[a]	Placebo TB2 (n=874)[a]
Deaths[b]	[redacted]	16 (1.9)[c]	10 (1.1)
Death considered related to treatment[d]	[redacted]	3 (0.4)	1 (0.1)
Participants with ≥1 serious AE[f]	[redacted]	148 (17.4)	138 (15.8)
Treatment discontinuations due to AEs	[redacted]	112 (13.1)	38 (4.3)
Study discontinuations due to AEs	[redacted]	69 (8.1)	32 (3.7)
Participants with ≥1 treatment-emergent AE[g]	[redacted]	759 (89.0)	718 (82.2)

[a]Participants may have been counted in more than 1 category; adverse events population is defined as all participants that received at least 1 infusion. [b]Deaths are also included under serious AEs and discontinuations due to AEs. [c]Includes 1 death that occurred after treatment completion and in the follow-up period. [d]Deaths related to donanemab occurred subsequent to ARIA and the death related to placebo occurred due to arteriosclerosis. [e]Value has been calculated. [f]Definition of serious AE: results in death, is life-threatening, required inpatient hospitalization or prolongation of existing hospitalization, results in persistent disability/incapacity, or based on other medical/scientific judgment. [g]Definition of treatment-emergent adverse event: an untoward medical occurrence that emerges during a defined treatment period, having been absent pre-treatment, or worsens relative to the pre-treatment state, and does not necessarily have to have a causal relationship with this treatment.
Abbreviations: AE: adverse event; TB2: TRAILBLAZER-ALZ 2.
Source: Sims *et al.* (2023)[5]; Eli Lilly Data on File.[141]

Table 14: Summary of treatment-emergent AEs ≥5% incidence by treatment group

Event, No. (%)	Donanemab All, Integrated Dataset (n=2,727)	Donanemab TB2 (n=853)[a]	Placebo TB2 (n=874)[a]
ARIA-E	[redacted]	205 (24.0)	17 (1.9)
ARIA-H	[redacted]	168 (19.7)	65 (7.4)
COVID-19	[redacted]	136 (15.9)	154 (17.6)
Headache	[redacted]	119 (14.0)	86 (9.8)
Fall	[redacted]	114 (13.4)	110 (12.6)
Infusion-related reaction	[redacted]	74 (8.7)	4 (0.5)
Superficial siderosis of central nervous system	[redacted]	58 (6.8)	10 (1.1)

Dizziness	[redacted]	53 (6.2)	48 (5.5)
Arthralgia	[redacted]	49 (5.7)	42 (4.8)
Urinary tract infection	[redacted]	45 (5.3)	59 (6.8)
Diarrhoea	[redacted]	43 (5.0)	50 (5.7)
Fatigue	[redacted]	42 (4.9)	45 (5.1)

[a]Participants may have been counted in more than 1 category; adverse events population is defined as all participants that received at least 1 infusion.
Abbreviations: AE: adverse event; ARIA-E; amyloid-related imaging abnormalities of oedema/effusions; ARIA-H: amyloid-related imaging abnormality of microhaemorrhages and hemosiderin deposits; NR: not recorded; TB2: TRAILBLAZER-ALZ 2.
Source: Sims *et al.* (2023)[5]; Eli Lilly Data on File.[141]

In the donanemab arm of the TRAILBLAZER-ALZ 2 trial, 3 participants with serious ARIAs subsequently died (2 were APOE ε4 heterozygous carriers and 1 was a noncarrier; none were prescribed anticoagulant or antiplatelet medications; 1 resumed treatment after resolution of severe ARIA of oedema/effusion that was accompanied by severe ARIA microhaemorrhages and hemosiderin deposits and 1 had superficial siderosis at baseline).

Either ARIA-E or ARIA-H occurred in 314 participants (36.8%) receiving donanemab and 130 (14.9%) receiving placebo. ARIA-E, determined via MRI, occurred in 205 participants (24.0%) in the donanemab group and in 18 (2.1%) in the placebo group. Most ARIA-E events were mild to moderate (n=188 [93.1%] in the donanemab group; n=17 [100%] in the placebo group). Table 15 presents a summary of ARIAs by treatment group for the TRAILBLAZER-ALZ 2 dataset. Note that there is high overlap in the patients with ARIA-E and ARIA-H, and therefore the events in the table for ARIA-E and -H are not mutually exclusive patients.

Table 15: Summary of ARIA by treatment group in the TRAILBLAZER-ALZ 2 trial[a]

Event, No. (%)	Donanemab TB2 (n=853)[b]	Placebo TB2 (n=874)[b]
Microhaemorrhage or superficial siderosis present at baseline, No.(%)	124 (14.5)	161 (18.4)
ARIA-E by APOE ε4 allele status, No./total No. (%)		
Noncarrier	40/255 (15.7)	2/250 (0.8)
Heterozygous carrier	103/452 (22.8)	9/474 (1.9)
Homozygous carrier	58/143 (40.6)	5/146 (3.4)
Any ARIA, No. (either -E or -H) (%)[c, d]	314 (36.8)	130 (14.9)
ARIA-E, No. (%)	205 (24.0)	18 (2.1)
Asymptomatic	153 (17.9)	17 (1.9)
Symptomatic	52 (6.1)	1 (0.1)[e]
ARIA-H, No. (%)	268 (31.4)	119 (13.6)
Microhaemorrhage	229 (26.8)	109 (12.5)
Superficial siderosis	134 (15.7)	26 (3.0)
Intracerebral haemorrhage >1cm	3 (0.4)	2 (0.2)

Footnotes: [a] Based on safety MRI or treatment-emergent AE cluster (after baseline); APOE-4 is a known risk factor for ARIA-E.

[b] Participants may have been counted in more than 1 category; adverse events population is defined as all participants that received at least 1 infusion.
[c] Based on MRI.
[d] There is high overlap in the patients with ARIA-E and ARIA-H, i.e. the events in table for ARIA-E and -H are not mutually exclusive patients.
[e] One placebo-treated participant had ARIA-E during the placebo-controlled period; however, the participant developed symptoms during the long-term extension period.
Abbreviations: AE: adverse event; APOE: apolipoprotein E; ARIA-E: amyloid-related imaging abnormalities of oedema/effusions; ARIA-H: amyloid-related imaging abnormality of microhaemorrhages and hemosiderin deposits; MRI: magnetic resonance imaging; TB2: TRAILBLAZER-ALZ 2.
Source: Sims *et al.* (2023)[5].

In the integrated dataset, 2 participants with serious ARIAs subsequently died. Based on MRI, either ARIA-E/H occurred in 819 of all donanemab participants ([redacted]%) in the integrated dataset. ARIA-E, determined by MRI occurred in 527 participants ([redacted]%).

A summary of ARIA events for the integrated dataset is presented in Table 16 below. Note that there is high overlap in the patients with ARIA-E and ARIA-H, and therefore the events in the table for ARIA-E and -H are not mutually exclusive patients.

Table 16: Summary of ARIA by treatment group in the integrated safety dataset

Event, No. (%)	Donanemab All, Integrated Dataset (n=2,727)
ARIA total events[a,*]	[redacted]
ARIA by MRI	[redacted]
Deaths[b]	[redacted]
SAEs*	[redacted]
Study withdrawal	[redacted]
Treatment Discontinuations	[redacted]
ARIA-E*	[redacted]
ARIA-E by MRI	[redacted]
Deaths[b]	[redacted]
SAEs*	[redacted]
Study withdrawal	[redacted]
Treatment Discontinuations	[redacted]
Symptomatic[c,*]	[redacted]
ARIA-H*	[redacted]
ARIA-H by MRI	[redacted]
Deaths[b]	[redacted]
SAEs*	[redacted]
Study withdrawal	[redacted]
Treatment Discontinuations	[redacted]
Symptomatic[c,*]	[redacted]

Footnotes: [a] Participants may be counted in more than 1 category. There is high overlap in the patients with ARIA-E and ARIA-H, i.e. the events in table for ARIA-E and -H are not mutually exclusive patients.
[b] Deaths are also included in SAEs and discontinuations due to an AE.
[c] Based on ARIA CRF for ARIA-E or AE reporting for ARIA-H.
* Based on MRI or TEAE cluster output.

Abbreviations: ARIA-E: amyloid-related imaging abnormalities of oedema/effusions; ARIA-H: amyloid-related imaging abnormality of microhaemorrhages and hemosiderin deposits; MRI: magnetic resonance imaging; SAE: serious adverse event.
Source: Eli Lilly Data on File.[141]

In the integrated dataset, the frequency of ARIA-E (based on MRI and TEAE cluster) was the highest in donanemab-treated homozygote APOE ε4 carriers:

- homozygote APOE ε4 carriers: [redacted]%
- heterozygote APOE ε4 carriers: [redacted]%
- noncarriers: [redacted]%

The frequency of symptomatic ARIA-E was the highest in donanemab-treated homozygote APOE ε4 carriers ([redacted]%). The frequency of serious ARIA-E was also the highest in donanemab-treated homozygote. APOE ε4 carriers ([redacted]%).

B.2.11 *Ongoing studies*

Additional data of interest for the efficacy and safety of donanemab to treat patients with early symptomatic AD are anticipated as summarised in Table 17, however none of the ongoing studies will provide evidence in the timeframe of this appraisal.

Table 17: Ongoing studies

Trial	Expected date of completion	Data of interest
TRAILBLAZER-ALZ 2 extension phase	Q4 2024	1-year follow-up of donanemab-treated patients beyond 18-months
TRAILBLAZER-ALZ 4	Q2 2024 (estimated availability of primary endpoint data)	Confirmatory data regarding amyloid plaque reduction
TRAILBLAZER-ALZ 6	Q4 2025 (estimated study completion)	Frequency and severity of ARIA-E and participant characteristics that may predict risk of ARIA

Abbreviations: ARIA: amyloid-related imaging abnormality; ARIA-E; amyloid-related imaging abnormalities of oedema/effusions.

B.2.12 *Interpretation of clinical effectiveness and safety evidence*

B.2.12.1 Principal findings from the clinical evidence base, highlighting key conclusions

The TRAILBLAZER-ALZ 2 trial demonstrated that donanemab was consistently associated with slowing AD clinical progression across all cognitive and functional endpoints tested, regardless of statistical model used. Donanemab treatment resulted in clinically meaningful benefit (considered

to be >20% slowing of clinical progression){{Sims, 2023 #18}} on the iADRS and CDR-SB scales, regardless of statistical model. Alongside the 37.4% risk reduction of disease progression as measured on the CDR-G score and the fact that an estimated 36% of participants receiving donanemab had no change in the CDR-SB at 1 year (no disease progression), compared with 23% of participants receiving placebo. Taken together, this could mean more time in the less impaired and more functional stages of AD, as well as a delay in the onset of a later stage decline.

In addition to slowing cognitive and functional decline, donanemab treatment resulted in significantly reduced brain amyloid plaque in participants as early as six months and at all time points assessed, with 76% participants within the overall population achieving amyloid clearance at 76 weeks. As discussed in Section B.3.2.2, growing evidence suggests that amyloid clearance impacts downstream pathologies and has important effects on clinical outcomes. Donanemab treatment also resulted in significantly reduced plasma P-tau217 level at 6 months and 12 months.

As seen in both the phase 2 TRAILBLAZER-ALZ trial and other trials of amyloid-lowering drugs, ARIA AEs were observed in the TRAILBLAZER-ALZ 2 trial. When ARIAs occurred, they were mostly asymptomatic and resolved in approximately 10 weeks. Whilst symptoms were usually mild, consisting of a headache or increase in confusion, more severe symptoms such as seizures were seen in some patients. For 1.6% of participants in the donanemab treatment group, ARIA led to serious outcomes, such as hospitalisation, and required supportive care and/or corticosteroid use, three participants with serious ARIAs in the donanemab group subsequently died.

As the trial allowed supportive care and non-disease modifying therapies to be taken alongside either donanemab or placebo, the placebo arm of the TRAILBLAZER-ALZ 2 trial can be considered an appropriate proxy for the comparator of relevance, BSC (Section B.1). Clinical experts in recent interviews have indicated that the number of patients on symptomatic treatments in the trial is roughly aligned to the general population. Adelphi real-world evidence data also supports this.[142]

B.2.12.2 Strengths and limitations of the clinical evidence base

TRAILBLAZER-ALZ 2 was a randomised, double-blind, placebo-controlled study which was appropriately powered to evaluate the safety and efficacy of donanemab in patients with MCI due to AD or mild AD.

Clinical experts consulted at an advisory board considered that the patients treated within TRAILBLAZER-ALZ 2 trial were similar in terms of baseline characteristics to patients expected to be seen in UK clinical practice. However, the population studied in the TRAILBLAZER-ALZ 2 trial was predominately white (ranging from 88.8% to 92.1%). This may limit the generalisability of the results to the population expected to be see in UK clinical practice as, according to the 2021 Census, 81.7% of the UK population are White, 9.3% are Asian, 4.0% are black, 2.9% mixed and 2.1% other ethnic groups.[143]

A strength of the TRAILBLAZER-ALZ trial programme is that symptomatic treatments (AChEIs and/or memantine) were allowed within the trials meaning that the trial more accurately reflects

patient experience in clinical practice. Research has demonstrated that worldwide, 18 to 35% of patients diagnosed with MCI due to AD receive AChEIs, and 7 to 8% receive memantine. In patients with mild AD dementia, 13 to 89% receive AchEIs and 1 to 21% use memantine.[144] In the GERAS study, 77.5% of 1,497 patients with AD were taking AchEIs.[145] However, due to the global nature of the trials and the difference in treatment guidelines across locations, the use of alternative treatments within the trial does not fully align with NICE guidelines. Use of these treatments was balanced between the donanemab and placebo treatment arms in the TRAILBLAZER-ALZ 2 trial.

Due to the 76-week trial duration, there are limited long-term efficacy and safety data for donanemab in AD, a life-long and life-limiting disease. Further data are being collected on the long-term effects of donanemab, however, these results will not be available during the timeframe of this appraisal.

B.2.12.3 Overall Conclusion

AD is a relentlessly progressive, neurodegenerative disorder for which no disease-modifying therapy is available. Donanemab significantly slowed clinical progression of AD at 76 weeks compared to placebo with improvements seen consistently across all cognitive and functional endpoints tested, regardless of statistical model. Donanemab will therefore help to address the high unmet need experienced by patients with MCI due to AD and mild AD dementia and allow patients to spend longer in less severe stages of the disease. The availability of a disease-modifying therapy could potentially have far-reaching implications and is likely to lead to the evolution of clinical care pathways in the NHS that will in turn, lead to overall improvements in the care provided for all patients with dementia.

B.3 Cost effectiveness

Summary of the cost-effectiveness analysis

- A *de novo* economic model was developed to assess the cost effectiveness of donanemab in the treatment of patients with either MCI due to AD or mild AD dementia and evidence of amyloid beta pathology
- The model adopted a Markov cohort state transition structure with five mutually exclusive health states: MCI due to AD, mild AD dementia, moderate AD dementia, severe AD dementia, and death
- The analysis was conducted from an NHS/PSS perspective, with a lifetime time horizon and costs and outcomes were discounted at 3.5% per annum
- Efficacy and safety data for donanemab were derived from the TRAILBLAZER-ALZ 2 trial, with treatment effect applied using hazard ratios of disease progression based on the CDR-SB scale.
- Utility values for the mild, moderate and severe AD dementia health states were sourced from the literature.[146] Utility values for MCI due to AD assumed equal to general population utility; this is a conservative approach as utility values for MCI due to AD from the literature were higher than general population values, and as such were not considered plausible. Caregiver utilities were also included in the model due to the high burden of AD on caregivers.

Base case cost-effectiveness results

- In the probabilistic analysis, donanemab was found to be cost-effective at PAS price compared to BSC at a willingness to pay (WTP) threshold of £20,000 per QALY, yielding an ICER of £16,203.38.
- The PSA found the probability of donanemab being cost-effective to be 63% and 87% at a WTP threshold of £20,000 and £30,000 per QALY, respectively.

Sensitivity and scenario analysis

- Deterministic sensitivity analyses (DSA) were conducted to assess uncertainty in the economic analysis and demonstrate that the base case cost-effectiveness results were robust to an extensive number of scenario analyses. The three most influential parameters in the model were the treatment effect versus BSC in mild AD dementia patients, the direct health and social care costs in severe AD dementia patients, and the relative dose intensity applied to donanemab treatment.
- Scenario analyses conducted to address sources of uncertainty in the model such as the treatment waning assumptions, distribution of diagnostic testing resources and different treatment stopping rules. The results of all probabilistic scenario analyses were comfortably under the £30,000 willingness-to-pay threshold, with the vast majority being below the lower end of the threshold range usually considered by NICE.

Conclusions

- The cost-effectiveness analysis demonstrates that donanemab represents a cost-effective use of NHS resources versus the available BSC options in England and is an important treatment option for patients with AD

B.3.1 *Published cost-effectiveness studies*

An economic SLR was conducted on the 12th October 2022, and updated on 4th September 2023, to identify all relevant literature published on previous economic evaluations, utility values and key model inputs to inform the cost effectiveness model of donanemab for the treatment of

early symptomatic AD. Full details of the economic SLR search strategy, study selection process and results are reported in Appendix E. When the results of the September 2023 SLR were combined with the results of the October 2022 SLR, a total of 56 articles reporting on 47 unique economic evaluations were identified by the SLR. Of these, four studies performed cost-utility analyses for approved AD treatments and emerging therapies from the UK-based perspective and four were UK-based economic model frameworks based on hypothetical new treatments for AD:

- The cost-effectiveness of donepezil, galantamine and rivastigmine for the treatment of patients with mild-to-moderate AD and memantine for the treatment of moderate-to-severe disease (Bond et al. 2012[147] and Peters et al. 2013[148])
- The cost-effectiveness of donepezil and the effects of early assessment (patients with undiagnosed AD entered the model) (Getsios et al. 2012)[149]
- The cost-effectiveness of continuing donepezil and commencing memantine (singly or in combination with donepezil) in patients with moderate-to-severe AD (MMSE 5-13) who had received donepezil for at least three months (Knapp et al. 2017)[150]
- The cost effectiveness of optimal treatment with memantine versus suboptimal AChEIs alone or no treatment for patients with moderate-to severe AD and AChEIs versus no AChEIs for patients with mild-to-moderate AD (Zala *et al*. 2018)[151]

Overall, none of the models identified in the SLR directly addressed the decision problem relevant to this submission and therefore a *de novo* economic model was developed.

B.3.1.1 Economic analysis

A *de novo* economic model was developed to assess the cost effectiveness of donanemab in the treatment of patients with either MCI due to AD or mild AD dementia and evidence of amyloid beta pathology.

The model was developed following the NICE 'Guide to the Methods of Technology Appraisal', the International Society for Pharmacoeconomics, Outcomes Research decision modelling guidelines and Society for Medical Decision Making taskforce good modelling practices, and the Canadian Agency for Drugs and Technologies in Health Guidelines for the Economic Evaluation of Health Technologies guidelines. Furthermore, considerations have been taken from NICE HTA Lab report.[21]

B.3.1.2 Patient population

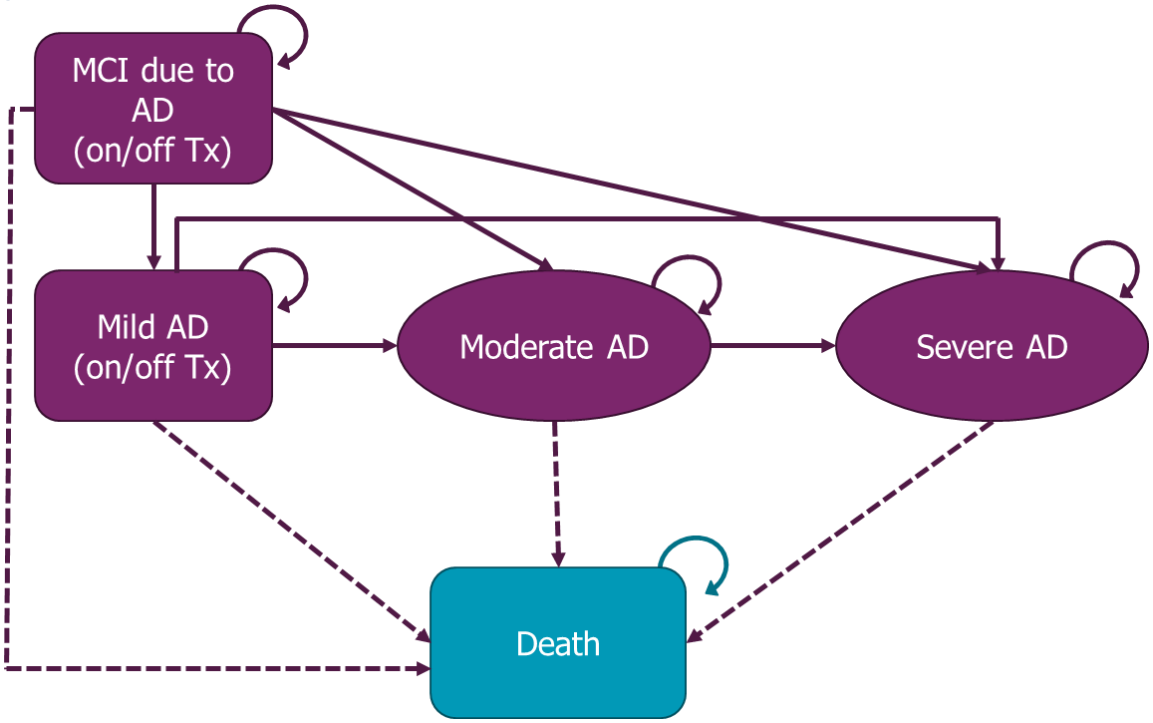
The economic analysis considered patients with MCI due to AD and mild AD dementia, in alignment with the modified-ITT population in the TRAILBLAZER-ALZ 2 trial. This population is reflective of the decision problem defined in Section B.1.1 and the expected marketing authorisation for donanemab.

B.3.1.3 Model structure

The cost-effectiveness model was constructed in Microsoft Excel and adopted a Markov cohort state transition structure with five mutually exclusive health states (Figure 13). The NICE HTA Lab report noted that a model investigating disease-modifying therapies for AD should be

"transparent and can be easily interrogated and validated within the evaluation timelines will increase the credibility of its outputs and be more informative for decision making." Additionally, the International PharmacoEconomic Collaboration on Alzheimer's Disease (IPECAD) modelling workshop challenge noted that due to the complexity of AD, it is important 'to balance simplicity and complexity in modelling it to capture the relevant key features of the disease without heavily relying on unvalidated data, statistical associations or assumptions'.[152] Therefore a transparent Markov model was adopted over a patient-level simulation model, as these are complex, have greater data requirements, and require increased model development, validation, and computational time.[153]

Figure 13: Model Structure



Abbreviations: AD: Alzheimer's disease; MCI: mild cognitive impairment; tx: treatment

The health states are based on disease stages and include: MCI due to AD, mild AD dementia, moderate AD dementia, severe AD dementia, and death. Please see section B.1.3 for more details on the progression of AD through these disease stages. While alive, patients could be either in a community setting or in residential care. It is assumed that the target patients with MCI due to AD or mild AD dementia are screened before entering the model for eligibility and as such, diagnostic costs are applied at the beginning of the model.

In each cycle, patients remain in their current state or progress to a more severe state. Patients either stop treatment according to the fixed treatment duration of 18 months or due to amyloid clearance at 6 or 12 months, with 90% of patients assumed to follow a fixed duration regimen and 10% of patients assumed to follow a treat-to-clear regimen. Patients were also assumed to stop receiving donanemab after progressing to the severe AD dementia health state. The maximum treatment duration for all patients was 18 months. The actual proportion of patients who stopped treatment due to amyloid clearance when following the treat-to-clear regimen was informed by TRAILBLAZER-ALZ 2 data; please refer to Section B.3.2.2 for more details on these

proportions. Patients can also discontinue treatment due to AEs. Patients were assumed to continue treatment in residential care.

Features of the cost-effectiveness analysis

The key features of the economic analysis and their justifications are presented in Table 18. Costs and health state utilities were allocated to each health state and multiplied by state occupancy to calculate the weighted costs and quality-adjusted life years (QALYs) per cycle, which were totalled at the end of the time horizon. Costs were in line with the NICE reference case perspective on costs and included:[1]

- drug acquisition
- drug administration
- diagnostic testing for identification of eligible patients
- monitoring for amyloid clearance during treatment period for the proportion treated according to this schedule (10% in the base case)
- safety monitoring and adverse event management (both ARIA and non-ARIA related), including MRI monitoring requirement
- concomitant medication
- disease management (patient and caregiver healthcare costs)
- residential care
- terminal care costs

Effectiveness measures included life years (LYs) and QALYs, and the incremental cost effectiveness ratio (ICER) of donanemab versus BSC without donanemab was assessed.

In line with the NICE reference case,[1] the perspective on costs was that of the National Health Service (NHS) and Personal Social Services (PSS). The perspective on outcomes was also in line with the NICE reference case, and include the health effects on patients and carers.[1] A lifetime time horizon was chosen. A 6-month cycle length was considered in the base case as this aligned with the time interval used for periodic assessment of amyloid clearance in the TRAILBLAZER-ALZ 2 trial. A half-cycle correction was applied. Costs and effects were discounted at 3.5% annually, in line with the NICE reference case.[1] Both patient and caregiver utility inputs were included in the model in order to measure the impact of the disease on the quality of life of both patients and caregivers, in line with the NICE reference case, which states that the perspective on outcomes should be all health effects for patients or carers.[1]

The economic analysis was conducted using recent estimates of resource use and treatment costs available from published sources, including NHS reference costs for 2021–2022 the British National Formulary (BNF), and the Monthly Index of Medical Specialties (MIMS).[154-156] All NHS reference costs were sourced for 2021/2022, which is the latest update for unit costs.[154] No inflation adjustment was applied to these costs as the most recently published Personal Social Services Research Unit's (PSSRU) NHS inflation index only covers up to 2021/2022.[157] However, inflation adjustments were applied for any costs from before 2022 according to the Consumer Prices Index including owner occupiers' housing costs (CPIH).[158]

Table 18: Features of the economic analysis

Factor	Previous models in AD	Current evaluation	
	TA217 (published 2011)[159]	Chosen values	Justification
Model structure	Markov model with three health states: pre- institutionalisation, institutionalisation and death	Markov model with five mutually exclusive health states: MCI due to AD, mild AD dementia, moderate AD dementia, severe AD dementia, and death.	The current model is designed for an amyloid targeting treatment, whereas the previous model was designed for symptomatic treatments, hence the different focus and nature of the model. Additionally, the model used in TA217 only considered patients with dementia, and did not include patients with MCI. The Markov model captures the relevant key features of the complex disease without heavily relying on unvalidated data, statistical associations or assumptions.
Time horizon	Lifetime (20 years)	Lifetime (28 years)	Given the nature of AD, a lifetime horizon was deemed necessary to capture all relevant costs and benefits.
Cycle length	Monthly	6 months with half-cycle correction	The cycle length was based on the time interval used for periodic assessment of amyloid clearance in the TRAILBLAZER-ALZ trials.
Treatment waning effect?	No specific treatment waning assumptions were included within the model.	Full treatment effect applied up to 5 years in total (1.5 years as observed in the clinical trial plus additional 3.5 years medium term treatment effect; total 10 cycles) A linear decreasing treatment effect from 5 years onwards up to 10 years with no remaining treatment effect (0%) after 10 years.	These assumptions are informed by the TRAILBLAZER-ALZ 2 trial,[11] and recent data from the TRAILBLAZER-ALZ trial on amyloid re-accumulation presented at AACI 2023,[160] and recent data from the TRAILBLAZER-EXT trial presented at AD/PD 2023.[161] Specifically, the overall amyloid level at Week 76 (average of 14.95 Centiloids) and the median re-accumulation rate of 2.8 Centiloids per year up to the threshold 24.1

			Centiloids, as well as the analysis on early completers at month 6 who have not been on treatment for the remaining 12 months of the trial due to the positive stopping rule
Source of utilities	The base-case model included patient utilities based on carer-proxy utility values. Self-reported patient utilities and carer utilities were included in the sensitivity analysis Carer utility associated with caring for patients with different CDR severities of Alzheimer's disease was mapped onto the MMSE scale	Patient utility values were sourced from Landeiro *et al*. 2020[146] Caregiver utility inputs were modelled by AD severity stage, based on two health state vignette studies which used a time trade-off approach to elicit utilities, as suggested by NICE guidelines when EQ-5D is not approriate.[1] The primary vignette,[162] used to inform health state utilities associated with being a caregiver of a person with MCI due to AD or mild AD, was conducted in 2023 and was developed with key opinion leaders (KOLs) and Alzheimer Europe. The secondary vignette study,[163] used to inform severe health states in the model, involved clinical expert interviews and caregiver and patient advocacy group representative interviews. Both studies also involved a literature review.	EQ-5D data were not collected in the TRAILBLAZER-ALZ 2 trial. QoL-AD data were collected for patients in the trial, but in a subset of patients. Therefore, patient utility values were instead sourced from the Landeiro *et al*. study, a meta-analysis of disease stage specific utilities that provides a higher level of evidence and reduces uncertainty around the point estimates than a single study would.[146] No data were collected on caregiver HRQoL in the trial. Therefore, two vignette studies were used to inform caregiver utilities, in line with NICE guidelines for when EQ-5D is not appropriate.[1]
Source of costs	Drug costs were based on the BNF[155] No adverse events or carer costs were included in the economic model	Drug costs of concomitant symptomatic medications were based on eMIT database of generic drugs and administration costs were sourced from NHS reference costs 2021/2022. Health state costs were derived from the PSSRU	To align with the NICE reference case.

		Adverse events were included in the economic model and costs were sourced from NHS reference costs 2021/2022	

Abbreviations: AD: Alzheimer's disease; Clinical Dementia Rating Scale – Sum of Boxes; ADCS-ADL: Alzheimer's Disease Cooperative Study – Activities of Daily Living Scale; BNF: British National Formulary; EQ-5D: EuroQoL-5 Dimension; HRQoL: health-related quality of life; MCI: mild cognitive impairment; MMSE: Mini-Mental State Exam; SLR: systematic literature review; TA: technology appraisal.

B.3.1.4 Intervention technology and comparators

Intervention

The intervention of interest is donanemab administered via intravenous infusion every 4 weeks. The initial three doses are of 700 mg, titrating up to 1400 mg from the fourth dose onwards. Donanemab should be administered over at least 30 minutes and patients should be observed post-infusion for a minimum of 30 minutes.

Treatment duration in the model can either be a fixed dose duration for 18 months or treat-to-clear for up to a maximum of 18 months. Within the base case this is assumed to be a ratio of 90%:10%, respectively. The base case ratio was estimated based on current diagnostic infrastructure in the UK (given the need for PET scans to confirm amyloid clearance) and was thought to be a realistic estimate by clinical experts. A treatment stopping rule was also included in the model for when a patient reaches a severe health state. It is likely that only small numbers of patients will meet this rule, given the population of interest and maximum treatment duration period of 18 months.

Use of approved symptomatic treatments for AD was permitted in TRAILBLAZER-ALZ 2, as per standard of care for AD. Therefore, the treatment intervention in the model is donanemab plus best supportive care (BSC).

Comparators

As discussed in Section B.1.2, donanemab is a unique treatment which targets the underlying pathology of AD, rather than only relieving symptoms. As such, there are no other treatment options in this positioning.

The model comparator therefore is established clinical management (referred to hereafter as BSC) without donanemab. Established clinical management for AD includes:

- For MCI due to AD:
    - Non-pharmacological management
    - Off-label symptomatic treatment for MCI due to AD (acetylcholinesterase inhibitor [AChEI]), consistent with real-world use[142]
- For mild dementia due to AD:
    - Non-pharmacological management
    - Symptomatic treatment for AD (AChEI or memantine)

Established clinical management for AD is discussed in further detail in Section B.1.3.4.

B.3.2 *Clinical parameters and variables*

B.3.2.1 Baseline characteristics

Baseline patient characteristics

The base case population within the model is aligned to the population in the TRAILBLAZER-ALZ 2 trial. Baseline patient characteristics for patients entering the model in MCI due to AD and mild AD dementia states are described in the Table 19 below. The initial distribution of patients across MCI due to AD and mild AD dementia states was 20.4% MCI due to AD versus 79.6% mild AD dementia, as informed by the TRAILBLAZER-ALZ 2 trial (overall population).

Table 19: Baseline patient characteristics

Parameters	MCI due to AD	Mild AD dementia	Source
Proportion female (%)	49.6%	57.0%	TB2 trial data on file (overall population)[106, 107]
Proportion in residential care (%)	0%	0%	No initiation of donanemab is assumed in residential care. Follow up treatment in residential care is possible within the model. However, this is considered to be minimal as within the first three cycles of the model, <2% of patients moved to residential care.
Age (years)	72.81 (SD, 5.79)	72.76 (SD, 6.23)	TB2 trial data on file (overall population)[106, 107]

Abbreviations: AD: Alzheimer's disease; MCI: mild cognitive impairment; NHS: National Health Service; SD: standard deviation; TB2: TRAILBLAZER-ALZ 2; UK: United Kingdom.

Caregiver baseline characteristics

Caregiver baseline characteristics informed the estimation of caregiver utility values and therefore caregiver QALYs. Mean caregiver age was used to inform age adjustment for caregiver utility values over time, based on the UK general population utility norm.[164]

The model differentiated between caregivers who are spouses of the patients and caregivers who are children of the patients. The age adjustment of utility values against general population norm was differentiated for each caregiver group based on the specified baseline age of the caregiver group as per the source. The proportion of child caregivers, and the mean age of child caregivers were informed by the GERAS study, an observational study of AD patients (N=1,497) and caregivers in France, Germany, and UK.[165]

Table 20: Baseline caregiver characteristics

Caregiver Characteristics	Values	Source
Child caregivers		

Caregiver Characteristics	Values	Source
Proportion of (child) caregivers (%)	29.1%	Reed 2014[166]
Mean age of (child) caregivers (years)	54.1 ± 8.1	
Proportion of male (child) caregivers (%)	25.4%	
Spouse caregivers		
Mean age of (spouse) caregivers (years)	73.4 ± 8.0	Reed 2014[166]
Proportion of male (spouse) caregivers (%)	41.2%	

Abbreviations: SD: standard deviation.

B.3.2.2 Treatment effect

Measure of treatment effect

Treatment effect is applied within the model using the hazard ratio of disease progression based on the CDR-SB measurement scale as described in Section B.2.3.1, applied to underlying disease natural history. Whilst iADRS is the primary measure in TRAILBLAZER-ALZ 2, CDR-SB is a well-established outcome measure that is more widely recognised.

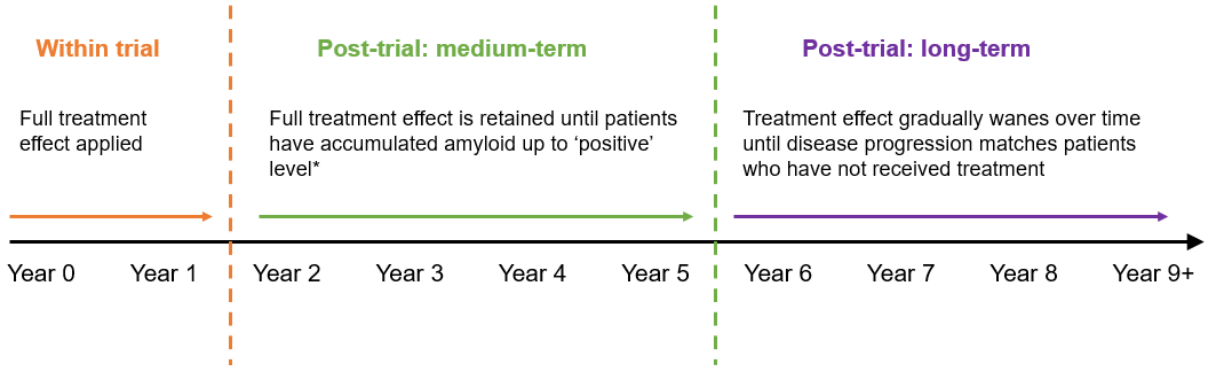
Treatment effect was not varied by disease stage within the model as disease severity is not considered a treatment effect modifier. This assumption is based on an interaction test completed using the CPH model described in Section B.2.6.5 investigating the interaction of AD severity by the study treatment variable. The results of this were not statistically significant with the p-value of the interaction of the AD severity category (screened according to the MMSE score) on the CDR-SB being 0.6286.

ApOE-4 homozygous status is also not considered to be a treatment effect modifier. Again, this assumption is based on an interaction test completed using the CPH model described in Section B.2.6.5, with the results of this analysis were not statistically significant

Modelling of treatment effect beyond treatment discontinuation (positive stopping rule)

Figure 14 illustrates the approaches to modelling the treatment effect used over the time horizon in the model. The time horizon is split into three parts: the trial period, post-trial (medium term) and post-trial (long term). It is assumed that the treatment effect of donanemab is maintained beyond treatment discontinuation (positive stopping rule) in the medium term and then begins to wane in the long term.

Figure 14: Conceptual approach to modelling of treatment effect



*Amyloid positivity is defined as an amyloid plaque level >24.1 CL.

Treatment effect within the trial period

The hazard ratio for disease progression based on the CDR-SB scale and derived from the TRAILBLAZER-ALZ 2 trial was used to model treatment effect for donanemab relative to BSC (B.2.6.5).[5] The calculated HR was applied to the natural history transition probabilities to more severe AD dementia states (Table 21).

Table 21: Hazard ratio of disease progression for donanemab versus BSC (CDR-SB scale)

HR vs. BSC	MCI due to AD, mild–moderate AD dementia	Severe AD dementia
Donanemab	0.62	n/a

Abbreviations: AD: Alzheimer's Disease; BSC: best supportive care; CDR-SB: Clinical Dementia Rating Scale – Sum of Boxes; HR: hazard ratio; MCI: mild cognitive impairment.

Treatment discontinuation and continued treatment effect

As discussed in Section 12 of the NICE HTA Lab report,[21] given that the maximum follow-up from the TRAILBLAZER-ALZ 2 trial is currently 18 months, estimates of treatment effectiveness need to be extrapolated beyond the trial time horizon over the lifetime of the patients. Assumptions were therefore made around the durability of the treatment effect based on clinical plausibility, expert opinion and the summary of evidence presented above, the model assumes a mid-term treatment effect before a gradual waning begins.

Summary of evidence on continued treatment effect following treatment discontinuation

The impact of completing active treatment on plaque re-accumulation was investigated by simulations in a treatment exposure–response (amyloid plaque) model using previously established methods.[167, 168] The model was based on data from four donanemab clinical trials (AACD [a phase 1 trial], TRAILBLAZER-ALZ 2, TRAILBLAZER-ALZ, and TRAILBLAZER-EXT) and predicted a median amyloid plaque re-accumulation rate of 2.8 Centiloids (CL)/year (95% CI 2.16 to 3.11).[160] These findings are supported by natural accumulation modelling studies,[169] showing approximately 3.3 Centiloids/year estimated rate of the natural amyloid accumulation model. Simulation results suggest that once amyloid is cleared, clinical efficacy is maintained after stopping treatment. This is likely due to the slow rate of re-accumulation of amyloid once it has been removed.

To evaluate the time course and sustainability of the reduction of amyloid plaque levels, the effect of donanemab versus placebo on brain amyloid deposition was assessed as a secondary objective within the TRAILBLAZER-ALZ 2 trial, by measuring change in brain amyloid plaque deposition via amyloid PET imaging from baseline through Week 76 (see Section B.2.6.3 for mean amyloid Centiloid levels at Week 76). Based on amyloid levels at Week 76 in TRAILBLAZER-ALZ 2 and assuming a reaccumulation rate of 2.8 CL, the time taken for a return to an amyloid plaque level >24.1 CL, which equates to amyloid positivity, after last treatment is approximately 3.5 years, assuming linear increase over time.

Within the emerging class of amyloid-targeting antibodies, growing evidence suggests that amyloid clearance impacts downstream pathologies and has important effects on clinical outcomes. Previously investigated amyloid-targeting agents such as solanezumab, gantenerumab, and bapineuzumab may have shown none to modest clinical benefit because of insufficient amyloid reduction.[115, 170-172] Newer therapies, such as donanemab, show more rapid and greater amyloid reduction.[4, 123, 173]

Figure 15 and Figure 16 provide group-level analyses showing the relationship between amyloid reduction and clinical outcomes seen in studies of gantenerumab, lecanemab, aducanumab, and donanemab. Both figures include the same data on the y-axis, the percent slowing relative to placebo for clinical outcomes from the last available time point in the placebo-controlled periods of the corresponding studies. The figures differ with respect to the data provided on the x-axis. Figure 15 includes the estimated 6-month CL value after 6 months of treatment, and Figure 16 includes the estimated CL reduction from baseline to the last available time point relative to placebo in the placebo-controlled period. The dotted linear regression line is weighted by the clinical measure treatment group sample size at the time point, represented by the scale of the circle. Gantenerumab, lecanemab, and aducanumab ENGAGE and EMERGE studies collected PET data via a sub-study; for a given circle in these studies, the amyloid PET result is based on the sub-study and the overall clinical measure result is based on the entire study population. The results from Figure 15 suggests that a lower level of amyloid level at 6 months of treatment is associated with better clinical outcome at study end (one year later except for gantenerumab 18 months later). that greater amyloid reduction at conclusion of the trial is associated with better clinical outcomes, with donanemab demonstrating both the largest amyloid plaque reduction and clinical benefits in the amyloid-targeting antibody class. Further, the effect of early amyloid clearance is also correlated with long-term outcomes.

Figure 15: Amyloid reduction at 6 months versus clinical outcome group-level at study conclusion in amyloid targeting therapies

The labels indicate the compound, phase, study, clinical measure time point and treatment arm. The size of the circle corresponds to the sample size of the clinical measure at the time point; the sample size was also used as a weight in the linear regression (dotted line). ADAS-Cog results are based on ADAS-Cog13 except for lecanemab, which uses ADAS-Cog14. Functional Measure results are based on ADCS-ADL-MCI in A3(1), A3(2) & L3; ADCS-ADL in G(I) & G(II); ADCS-iADL in D2 & D3; and FAQ in G3 (SR). Results are based on MMRM models where available. Values were approximated from figures if not reported directly.
Abbreviations: A3(1): Aducanumab Ph3 301; A3(2): Aducanumab Ph3 302; ADAS-Cog13: Alzheimer's Disease Assessment Scale – 13-item Cognitive Subscale; ADCS-iADL: Alzheimer's Disease Cooperative Study – instrumental Activities of Daily Living subscale; D2: Donanemab Ph2 TRAILBLAZER-ALZ; D3: Donanemab Ph3 TRAILBLAZER-ALZ2 (low-medium tau population); G3(I): Gantenerumab Ph3 GRADUATE I; G3(II): Gantenerumab Ph3 GRADUATE II; G3(SR): Gantenerumab Ph3 SCarlet RoAD; L2: Lecanemab Ph2; L3: Lecanemab Ph3 CLARITY; mpk: mg/kg; Q2W: biweekly; Q4W: monthly; M: month; MMRM: mixed model for repeated measures; Ph: phase; PET: Positron emission tomography.
Source: Data on File.[174]

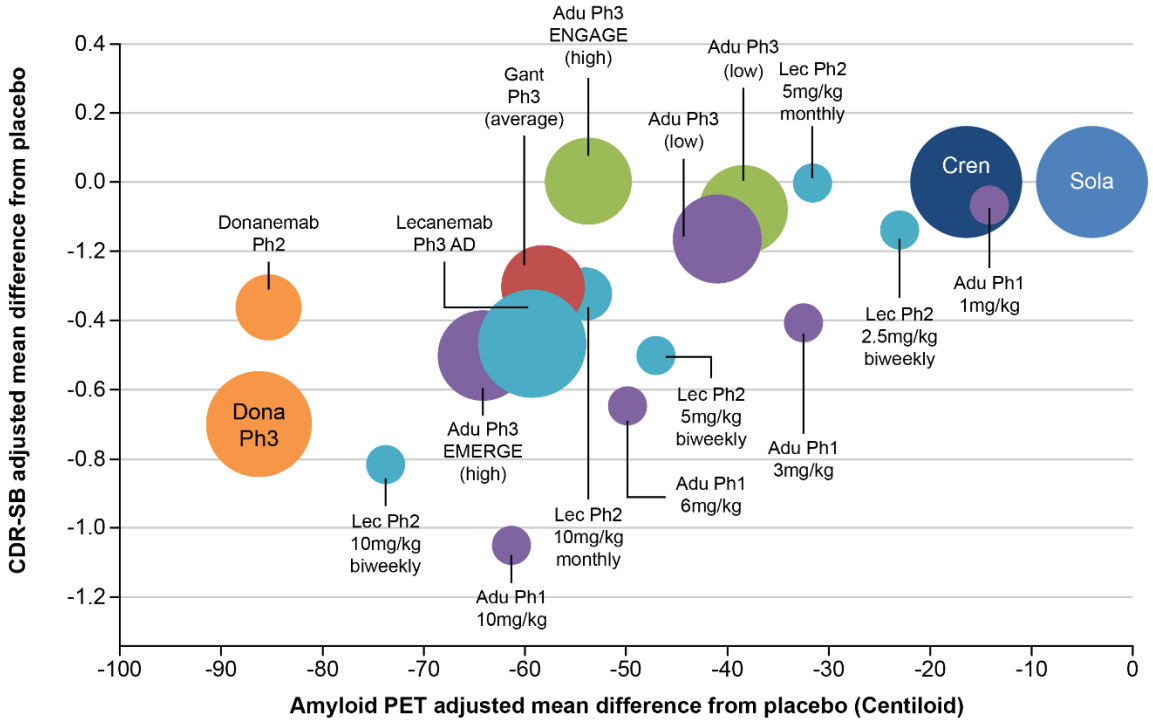
Figure 16: Amyloid reduction versus clinical outcome group-level at study conclusion in amyloid targeting therapies

The labels indicate the compound, phase, study, clinical measure time point and treatment arm. The size of the circle corresponds to the sample size of the clinical measure at the time point; the sample size was also used as a weight in the linear regression (dotted line). ADAS-Cog results are based on ADAS-Cog13 except for lecanemab, which uses ADAS-Cog14. Functional Measure results are based on ADCS-ADL-MCI in A3(1), A3(2) & L3; ADCS-ADL in G(I) & G(II); ADCS-iADL in D2 & D3; and FAQ in G3 (SR). Results are based on MMRM models where available. Values were approximated from figures if not reported directly.

Abbreviations: A3(1): Aducanumab Ph3 301; A3(2): Aducanumab Ph3 302; ADAS-Cog13: Alzheimer's Disease Assessment Scale – 13-item Cognitive Subscale; ADCS-iADL: Alzheimer's Disease Cooperative Study – instrumental Activities of Daily Living subscale; D2: Donanemab Ph2 TRAILBLAZER-ALZ; D3: Donanemab Ph3 TRAILBLAZER-ALZ2 (low-medium tau population); G3(I): Gantenerumab Ph3 GRADUATE I; G3(II): Gantenerumab Ph3 GRADUATE II; G3(SR): Gantenerumab Ph3 SCarlet RoAD; L2: Lecanemab Ph2; L3: Lecanemab Ph3 CLARITY; mpk: mg/kg; Q2W: biweekly; Q4W: monthly; M: month; MMRM: mixed model for repeated measures; Ph: phase; PET: Positron emission tomography.
Source: Data on File.[174]

A similar analysis found that change in CDR-SB was also correlated with amyloid PET centiloid difference in change over time when considering donanemab, lecanemab, aducanumab and solanezumab (Figure 17).[130]

Figure 17: Amyloid plaque reduction correlated with clinical benefit (CDR-SB)



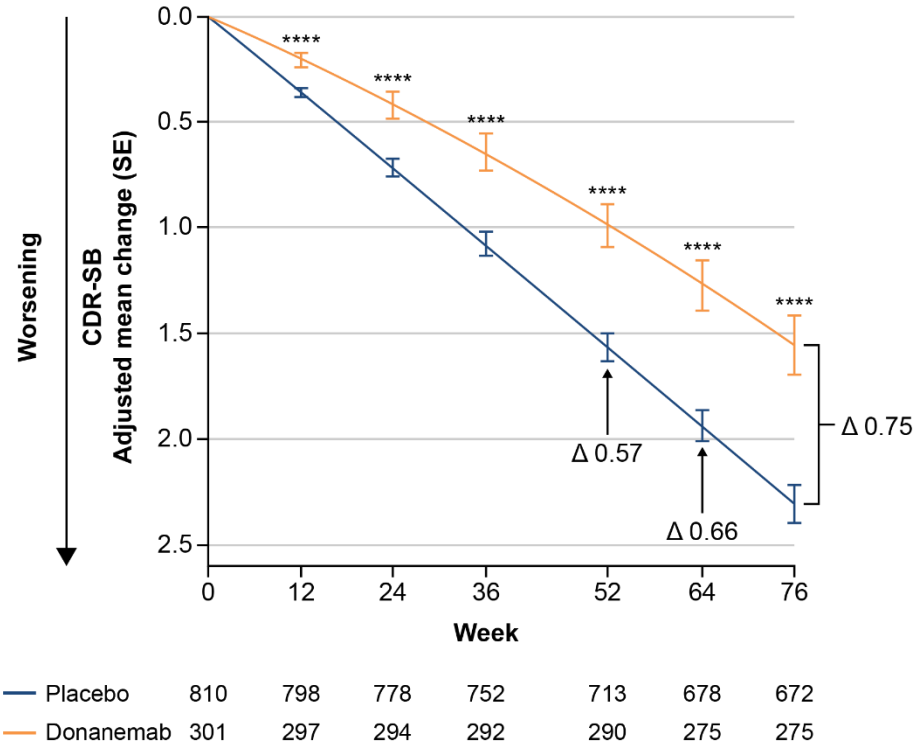
Abbreviations: CDR-SB: Clinical Dementia Rating Sum of Boxes; PET: Positron emission tomography.
Source: Adapted from Boxer *et al.* (2023). [130]

Summary of evidence on continued treatment effect in patients discontinuing treatment due to amyloid clearance

A subgroup analysis evaluated clinical progression among participants in the overall population who achieved early amyloid clearance (<24.1 CL) at 24 or 52 weeks and so switched to placebo treatment in a blinded manner. The median time in trial prior to placebo switch was 47 weeks, meaning that patients were off treatment for 29 weeks. It was demonstrated that in these individuals, there was a significant slowing of clinical progression at Week 76 as measured by the CDR-SB (Figure 18), which was comparable to that observed in participants who continued treatment after 24 weeks. The treatment effect versus placebo continued to widen over time among donanemab-treated participants who switched to placebo at 24 or 52 weeks. These data support the assumption

that treatment effect is not lost immediately after treatment is stopped and continues beyond treatment discontinuation.

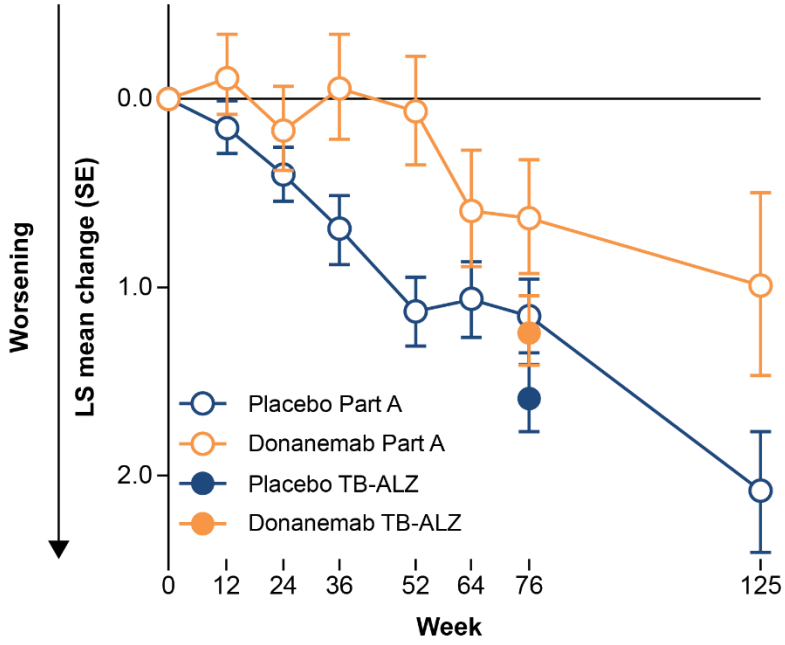
Figure 18: Change from baseline to Week 76 (CDR-SB) in patients who discontinued treatment at 6-months or 12-months due to amyloid clearance



Abbreviations: CDR-SB: Clinical Dementia Rating scale Sum of Boxes; SE: standard error.
Source: Adapted from Sims *et al.* (2023).[5]

The assumption on maintenance of effect in the medium term (Figure 19) is further supported by data from the TRAILBLAZER-EXT (NCT04640077), a phase 2 donanemab long-term follow-on study in which TRAILBLAZER-ALZ participants originally randomised to placebo received donanemab, and participants originally randomised to donanemab participated in a long-term follow-up visit with no treatment. Part A of the long-term extension evaluated the reliability of video teleconference compared with on-site administered cognitive and functional measures at Week 125. Although limitations include relatively small n (25, 58), returner bias (impact in placebo group), most Part A scales performed after TRAILBLAZER-ALZ treatment assignments known, the data suggest a maintenance of treatment effect.

Figure 19: Clinical scales ~1 Year post donanemab treatment in TRAILBLAZER-EXT Part A: CDR-SB



Placebo Part A n=58	58	51	56	58
Donanemab Part A n=25	24	21	25	25

Abbreviations: CDR-SB: CDR-SB: Clinical Dementia Rating scale Sum of Boxes; LS: least square; SE: standard error.
Source: Adapted from Evans *et al*. (2023).[161]

Treatment effect assumptions made within the model (short/medium term)

In the model, it was assumed that patients had the full magnitude of treatment effect if they were on treatment. Once patients were off treatment, different assumptions around treatment effect waning and duration were applied based on specific discontinuation scenarios (Table 22).

These assumptions differed between patients who discontinued treatment due to positive stopping rules and those who discontinued due to negative stopping rules. Positive stopping rules included treatment discontinuation due to fixed treatment duration or due to amyloid clearance. Negative treatment stopping rules included discontinuation due to progression to the severe health state and discontinuation due to adverse events (AE).

Table 22: Discontinuation scenarios used within the model

	Discontinuation rule	Base case
Positive stopping rule	Due to fixed treatment duration (18-months) Due to amyloid clearance at month 6 or month 12 defined as <24.1 CL at any amyloid PET scan.	Patients retain full treatment effect for the fixed treatment duration (18 months). Based on amyloid levels at Week 76 in TRAILBLAZER-ALZ 2 and using a reaccumulation rate of 2.8 CL,[160] the time taken for a return to an amyloid plaque level >24.1 CL, which equates to amyloid positivity, after last treatment is approximately 3.5 years, assuming linear increase over time. Hence, the base case assumes that full treatment effect would then be retained until 5 years. Clinical opinion suggests that it is not plausible that treatment effect of donanemab would be immediately lost upon return to amyloid positivity, the threshold of which is far lower than mean amyloid levels at baseline. It was therefore assumed that the treatment effect gradually wanes to zero over a further period of 5 years.
Negative stopping rule	Discontinuation due to progression to severe AD dementia	For the base case, severe AD was set as limit state for donanemab. Once these patients have discontinued treatment, they regress to natural history progression (HR for AD progression = 1).
	Discontinuation due to AEs (mainly ARIA and IRRs)	For patients who permanently discontinue treatment due to AEs, model retains full treatment effect for 2 cycles (12 months) After 12 months, treatment waning was assumed for 5 cycles (2.5 years) and 0% treatment effect was assumed at the end of the treatment waning period.
Treatment interruption	For a proportion of patients who experience ARIA, treatment is paused for a duration before re-initiation.	In the model, the RDI for donanemab was adjusted to account for a proportion of patients for whom treatment was interrupted due to ARIA with the duration of treatment interruption as observed from the TB2 trial.[5] The RDI is intended to represent the ratio between the dose effectively administered and the target dose. An overall RDI of 95.11% was applied for donanemab, calculated as a weighted average based on the following inputs: the proportion of patients for whom treatment was interrupted due to ARIA (36.8%), the mean duration of treatment interruption as observed from the TB2 trial (72.4 days, or about two doses), and the trial duration (18 months or 19.55 28-day dosing cycles), informed by TB2 data.

Abbreviations: AD: Alzheimer's disease; AE: adverse event; ARIA: amyloid-related imaging abnormalities; CL: Centiloid; HR: hazard ratio; IRR: infusion-related reaction; PET: positron emission tomography; RDI: relative dose intensity; TB2: TRAILBLAZER-ALZ 2.

The inputs used to inform the proportion of patients who discontinue treatment due to amyloid clearance for donanemab is presented in Table 23. The remaining patients are not screened for amyloid clearance at baseline and as such stop treatment at 18-months.

Table 23: Proportion of patients stopping treatment due to amyloid clearance

Parameter	Base-case value	Source
Percentage of patients screened for amyloid clearance at baseline	10%	Assumption based on current availability of PET scanners within the UK
Percentage of screened patients who stop treatment due to amyloid clearance at each timepoint*	6 months: 29.70% 12 months: 36.42%	TB2 trial (overall population)[5]

Footnotes: Patients who do not report clearance through a PET scan will stop treatment at 18-months (the fixed-treatment duration) and costs of amyloid PET are not applied at this timepoint.
Abbreviations: PET: Positron emission tomography; TB2: TRAILBLAZER-ALZ 2.

B.3.2.3 Disease progression

In the model, the natural history of disease progression is informed by transition probabilities between health states defined on the CDR-SB scale of the prevalent cohort (n=3,334) in line with routine clinical practice.

Data from National Alzheimer's Coordinating Centre (NACC) were used to estimate annual transition probabilities among recent prevalent and incident cohorts of individuals with biomarker-confirmed early AD using CDR-SB; transition probability calculations did not allow participants to experience an improvement in their disease. A multinomial logistic regression model was fitted using maximum likelihood and was used to calculate the annual transition probabilities from one disease state to another disease state conditional on the initial state. The multinomial model produced a transition equation for each pair of consecutive visits, which relates the predictors to the probability of transitioning to a given health state via the estimated model coefficients. The transition probability equations were then used to calculate mean transition probabilities for each pair (and associated 95% Cis) by holding constant age, sex, and time between visits.

Table 24 presents transition probabilities from the NACC analysis based on the CDR-SB matching the baseline patient age (73 years old) and percentage of females (55%) of the overall population in TB2.

Table 24: Annual health state transition probabilities (NACC analysis—CDR-SB)

To From	MCI due to AD	Mild dementia due to AD	Moderate AD dementia	Severe AD dementia	Dead
Base case: CDR-SB					
MCI Due to AD	71.1% (69.7%, 72.6%)	26.4% (24.9%, 27.8%)	1.4% (1.0%, 1.7%)	0.2% (0.1%, 0.2%)	1.0% (0.7%, 1.2%)
Mild Dementia Due to AD	0.0% (0.0%, 0.0%)	64.8% (63.2%, 66.4%)	29.7% (28.2%, 31.2%)	2.9% (2.3%, 3.4%)	2.6% (2.1%, 3.1%)
Moderate AD Dementia	0.0% (0.0%, 0.0%)	0.0% (0.0%, 0.0%)	57.4% (55.1%, 59.7%)	32.3% (30.2%, 34.5%)	10.3% (8.9%, 11.6%)

Severe AD Dementia	0.0% (0.0%, 0.0%)	0.0% (0.0%, 0.0%)	0.0% (0.0%, 0.0%)	70.7% (68.5%, 72.9%)	29.3% (27.1%, 31.5%)

Abbreviations: AD: Alzheimer's disease; CDR-SB: Clinical Dementia Rating Scale – Sum of Boxes; MCI: mild cognitive impairment;; NACC: National Alzheimer's Coordinating Centre.

In the model, transition probabilities informing natural history of disease progression were rescaled to the 6-month model cycle length as follows:

- The probability of transitioning out of any given state was converted to an exponential rate that was scaled to align with the cycle length.
- The scaled rates were then reconverted to the probabilities.
- The probabilities for remaining in the same state (i.e., the probabilities on the principal diagonal of the trace matrix) were calculated as the difference between 100% and the row sums of scaled probabilities to ensure that the transition probabilities from each state sum to 100%.

The transition matrix was re-calculated for each timepoint in the calculations to account for the varying probability of death based on the patient's age.

The study assumed no change in progression risk over time. If supported by evidence, use of time-dependency progression rate from MCI due to AD dementia would be expected to favour ATTs, as an acceleration in progression rates with time would mean that delaying progression would have a larger impact.

Scenarios were also tested using transition probabilities obtained from Potashman *et al*. (2021)[175] (Table 25 and Table 26). The same approach converting annual probabilities to 6-month probabilities was also applied to alternate data sources options. A recent study by Potashman *et al*. (2021)[175] provides a transition matrix for all stages from asymptomatic to death for individuals with AD dementia pathology. The estimated annual progression rates were based on patient-level longitudinal data from the NACC Uniform Data Set (UDS) which consisted of 3,291 incident patients and 4,370 prevalent patients from 2005 to 2017. The CDR-SB scores were used to define the AD dementia stage (0, 0.5–4.0, 4.5–9.0, 9.5–15.5, and 16.0–18.0 for asymptomatic, MCI due to AD, mild AD dementia, moderate AD dementia, and severe AD dementia, respectively) and generate the transition probabilities. The study reported transition probabilities for incident and prevalent population, and the authors indicated that the latter may have been overestimated when compared with the former because the time spent by the prevalent patients before entering the NACC data set may have been missed. Therefore, the model used probabilities observed for the incident population adjusted for the requirements of the model (Table 25).

Because transition probability values for asymptomatic patients are not required in the current model, the percentage transitioning to asymptomatic reported by Potashman *et al*. (2021) was distributed proportionally to the remaining transition probabilities so the transition probabilities from each health state summed up to 100%. In addition, the observed small regression probabilities were added to the probability of staying in the same state in the base case. Lastly, probabilities for transition to residential care were not reported in this study.

Table 25: Annual health state transition probabilities (Potashman 2021)

To From	Asymptomatic	MCI due to AD	Mild AD dementia	Moderate AD dementia	Severe AD dementia	Dead
MCI Due to AD	5.3%	68.2%	15.9%	5.7%	0.2%	4.7%
Mild AD Dementia	0.0%	3.0%	51.8%	31.6%	4.3%	9.2%
Moderate AD Dementia	0.0%	0.0%	1.8%	38.4%	28.6%	31.2%
Severe AD Dementia	0.0%	0.0%	0.0%	1.3%	52.0%	46.7%

Abbreviations: AD: Alzheimer's disease; MCI: mild cognitive impairment.
Source: Potashman *et al*. (2021)[175] (Table 3 Annual transition probabilities among the incident population with amyloid restriction)

Table 26: Annual health state transition probabilities (Potashman 2021; excluding asymptomatic and regression probabilities)

To From	MCI due to AD	Mild AD dementia	Moderate AD dementia	Severe AD dementia
MCI Due to AD	77.1%	16.7%	6.0%	0.2%
Mild AD Dementia	3.3%	57.1%	34.8%	4.7%
Moderate AD Dementia	0.0%	2.6%	55.8%	41.6%
Severe AD Dementia	0.0%	0.0%	2.4%	97.6%

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

Risk of institutionalisation

Annual probabilities for transition to the institutionalisation setting were applied based on the values presented in Table 27. No risk of institutionalisation was assumed for MCI due to AD due to limited evidence in literature and minimal impact on the outcomes.

Table 27: Risk of institutionalisation

Disease stage	Annual probability of institutionalisation
MCI Due to AD	0.00%
Mild AD Dementia	1.20%
Moderate AD Dementia	3.40%
Severe AD Dementia	6.60%

Abbreviations: AD: Alzheimer's disease; MCI: mild cognitive impairment.
Source: Spackman et al. (2012).[176]

B.3.2.4 Adverse events

ARIA events have been observed after treatment with amyloid-targeting therapies and are therefore important AEs for consideration with these therapies. As such, all-grade events for ARIA were considered in the model. For other treatment-related AEs, IRRs, and hypersensitivity, moderate and severe events were included.

As most ARIA events occur within the first 3–6 months of treatment initiation, the rate of ARIA events observed from the trial were applied during the first cycle (6 months) in the model.[177] The

rates for IRR, hypersensitivity and anaphylactic reaction were reported for the entire trial period, and were converted to 6-month probabilities aligned with the model cycle-length and used in the model calculations.

In clinical practice, patients may stop treatment due to ARIA events, anaphylaxis, IRRs or hypersensitivity. Discontinuation due to AEs was implemented in the base case for all treatment arms, using discontinuation due to AE incidence data (13.10%) from the TRAILBLAZER-ALZ 2 trial.[5]

AEs were not considered for the BSC arm in the model, although ARIA-E/H were observed in the placebo arm of the TRAILBLAZER-ALZ 2 trial. [5] More weight is therefore placed on the AEs for the treatment arm than observed in the trial, making this approach conservative. AE rates for donanemab were informed using the TRAILBLAZER-ALZ 2 trial data. The incidence of AE included in the model for patients receiving donanemab within the model are reported in Table 28.

Table 28: AE incidence

Treatment	ARIA-E and/or ARIA-H		IRR	Hyper-sensitivity	Anaphylactic reaction (all grades)
	Trial reported overall incidence	% of symptomatic events			
Donanemab	36.80%	25.37%*	3.75%	0.82%	0.35%

*Rate of symptomatic ARIA events is based on ARIA-E cases and assumes the same rate for ARIA-H.
Abbreviations: AE: adverse event; ARIA: amyloid-related imaging abnormalities; ARIA-E: ARIA with edema/ effusion; ARIA-H: ARIA with haemorrhages; IRR: infusion-related reaction.

B.3.2.5 Mortality

Within the model, a hazard ratio for mortality is applied for patients with AD dementia relative to the general population (Table 29). No difference in mortality was assumed between the community and residential care settings.

Table 29: Mortality risk for patients with AD compared to general population

Health state	Risk of mortality
MCI due to AD	1
AD dementia	2.55

Abbreviations: AD: Alzheimer's Disease; MCI: mild cognitive impairment.
Source: Office for National Statistics (2023)

There is a small mortality risk associated with donanemab treatment (0.35%) that is applied at the end of the first cycle.[5]

B.3.3 *Measurement and valuation of health effects*

In the model, health state utility values were informed by estimates from the literature, as detailed in Section B.3.3.5 and Appendix E.

B.3.3.1 Health-related quality-of-life data from clinical trials

No EQ-5D data were collected in the TRAILBLAZER-ALZ trials. HRQoL data were instead collected using the Quality of Life in Alzheimer's Disease (QoL-AD) questionnaire in a subset of the total TRAILBLAZER-ALZ 2 sample. HRQoL data are presented in Section B.2.6.4.

B.3.3.2 Mapping

No mapping techniques were employed as part of this cost-effectiveness analysis. As described in Section B.3.3.1, no EQ-5D were captured as part of the TRAILBLAZER-ALZ 2 trial, with QoL-AD data collected instead. It was not considered appropriate to attempt to map these data to EQ-5D for the following reasons:

- Due to its 18-month duration, the TRAILBLAZER-ALZ 2 trial was not considered sufficiently long enough to adequately capture the disease severity of AD. Any mapped analysis would therefore need to be supplemented with literature to cover the more severe health states
- HRQoL data collection within the TRAILBLAZER-ALZ 2 trial was only done within a subset of the patient population and as such, may not be reflective of the entire patient population
- The use of data from one study is associated with greater uncertainty given the patient population and noise in the data, therefore a meta-analysis was instead considered preferable
- Data on caregiver QoL were not collected within the TRAILBLAZER-ALZ 2 trial

B.3.3.3 Health-related quality-of-life studies

As described in Section B.3.1, an SLR was conducted to identify relevant literature published on previous economic evaluations, utility values and key model inputs to inform the cost effectiveness model for donanemab. The utilities SLR yielded 34 publications which reported on 30 unique studies on utility outcomes for patients with AD, as described in Appendix E.

The utility studies used within the cost-effectiveness analysis are described in Section B.3.3.5.

B.3.3.4 Adverse events

Disutilities associated with AEs were applied in the model. In the model, a disutility for all symptomatic ARIA events was applied for the average duration of such events as a one-time utility decrement. Since headache was the most reported symptom among patients with symptomatic ARIA, the disutility value for a headache (–0.14), in the case of a headache in the UK as obtained from Xu *et al*. 2011) was used as a proxy for ARIA disutilities.[178] A utility decrement was applied for anaphylactic reaction (–0.118) based on a 15% reduction in baseline utility.[179] For recurrent AEs (IRRs & hypersensitivity), no utility decrement was applied as in clinical practice, patients would be effectively treated for these AEs and the cost of treating these AEs are included within the model. Only moderate and severe IRR events were considered as mild cases of IRR would be handled by slowing down the rate of infusion.

Disutility values for AEs were sourced from published literature and are presented in Table 30.

Table 30: AE disutility values

Adverse Event	Disutility	Duration (Days)	Source
ARIA event	−0.14	72.40 days	Xu 2011[178]; Duration: mean time to resolution in TB2[5]
Anaphylactic reaction	−0.118	30 days	Hannouf 2012[179] Calculated as 15% reduction in baseline utility (weighted average of MCI due to AD and mild AD)

Abbreviations: ARIA: amyloid-related imaging abnormalities; ARIA-E: amyloid-related imaging abnormality of oedema/effusions; ARIA-H: amyloid-related imaging abnormality of microhaemorrhages and hemosiderin deposits; TB2: TRAILBLAZER-ALZ 2.

B.3.3.5 Health-related quality-of-life data used in the cost-effectiveness analysis

In order to measure the impact of the disease on the quality of life of both patients and caregivers, patient and caregiver utility inputs were modelled by AD severity stage.

Patient utilities

Patient utility values were applied from Landeiro *et al*. 2020,[146] an SLR and fixed-effect meta-analysis of HRQoL of people with AD dementia that reported weighted averages of carer rating of patient HRQoL measured by EQ-5D, by AD dementia severity. It is assumed within the model that health state utility values do not differ by setting (i.e. community or residential care).

The Landeiro review found limited published data on HRQoL for patients with MCI due to AD.[21] A previously published study by Aye *et al*. (2023) measured health utility values for MCI due to AD patients and reported a utility value of 0.81 for MCI due to AD patients.[180] In the model, a conservative approach was used, applying a general population utility value (0.76) for MCI due to AD patients based on mean age (78.40 years) and proportion of female patients (58.5%) in the utility source (i.e., Landeiro 2020), to be comparable to the utility values of other AD states generated from the same study.

Table 31 shows average utility values reported in Landeiro *et al*. 2020 that are used within the model.[146] As these utilities were obtained from a population different from the TRAILBLAZER-ALZ 2 trial, these utilities were adjusted to match the characteristics in terms of age of the TRAILBLAZER-ALZ 2 trial, correcting for differences between the trial and the utility data source. To do this, the utilities were multiplied by an adjustment factor created by accounting how the general population utilities change based on age, so that the final utilities used in the model are estimated for a population with the same age composition as in the trial, and are continually adjusted for age as the model progresses.

Table 31: Summary of patient utility values for cost-effectiveness analysis

State	Utility value: mean (standard error)		Source
	Community setting	Residential setting	
MCI due to AD	0.76	0.76	Based on general population utility values aligned with

			baseline age and % female
Mild AD dementia	0.74	0.74	Landeiro *et al.* (2020)[146]; weighted mean using the fixed-effect method
Moderate AD dementia	0.59	0.59	
Severe AD dementia	0.36	0.36	

Abbreviations: AR: adverse reaction; CI: confidence interval; HS: health state

Caregiver utilities

Caregiver utilities are important to consider in this appraisal due to the high burden of AD on caregivers. As detailed in Section B.1.3.2, many patients with AD are cared for by family members, friends, or another unpaid care partner and the emotional burden of caring for a loved one with AD is substantial.[181] In a 2019 global survey: care partners reported that their health (52% of respondents), work (49%), and social life (62%) had suffered as a result of their role, and 75% of care partners said they felt stressed about caring and about meeting their other responsibilities.[182] Data from the GERAS study show that the burden of caring for a loved one with AD increases as the disease progresses.[183]

Recent research has indicated that EQ-5D data may not be sensitive to the unique impact experienced by AD caregivers.[184] The research demonstrated that the EQ-5D index score had a low sensitivity to change over an 18-month period suggesting the EQ-5D was not sensitive to change in QoL across the AD dementia severity range. These results indicate that the EQ-5D is perhaps not particularly an appropriate measure for effectively capturing the impact of caring for people with AD dementia on caregivers. Therefore, caregiver utility values were applied in the model, derived from two vignette studies conducted by Lilly based on a time trade-off approach; as is recommended by NICE for situations in which use of EQ-5D is not appropriate.[1, 162, 163]

The primary vignette study, 'Assessment of Utilities Associated with Being a Caregiver of a Person with Alzheimer's Disease'[162] was conducted to derive health state utilities associated with being a caregiver of a person with MCI due to AD or mild AD. This health state vignette was conducted using a robust time trade-off approach to maximize comparability both across studies and to the methods used to value the EQ-5D health states, in line with the NICE reference case guide for when EQ-5D data are not appropriate.[1] A pilot phase was first conducted to ensure the health states and methodology of the main phase were comprehensible and feasible, using participant feedback to revise the health states.[162] For the main phase, interviews were conducted in 304 general population participants across 4 locations in the UK (London, Bath, Leeds and Edinburgh). In this study, the categories of 'spouse caregiver' and 'child caregiver' were used as a proxy for whether the carer is living with the patient or not, i.e. spouse caregivers were assumed to live with the patient, whereas child caregivers were assumed not to live with the patient.

A second vignette study, 'The Impact of Informal Caregiving in Alzheimer's Disease Dementia: A Health Utility Study in the United Kingdom' (for which, data collection took place in Q1 2016) was used to inform severe health states in the model.[163] The severe utility was adjusted for the difference observed between the moderate health states of this and the primary vignette studies, given the time gap between the studies.

The caregiver utility values considered in the base case are presented in Table 32.

Table 32: Base-case value for caregiver utilities

Caregiver utilities (EQ-5D)	Mean (SD)	Source
Child Caregiver - Community Setting		
MCI due to AD	0.84 (0.18)	Data on file, 2023[162]
Mild AD dementia	0.78 (0.20)	Data on file, 2023[162]
Moderate AD dementia	0.62 (0.32)	Data on file, 2023[162]
Severe AD dementia	0.46 (0.30)	Adjusted, Belger *et al*. 2022[163]
Child Caregiver – Residential Care Setting		
MCI due to AD	0.84 (0.18)	Assumed same as community setting
Mild AD dementia	0.78 (0.20)	Assumed same as community setting
Moderate AD dementia	0.71 (0.25)	Belger *et al*. 2022[163]
Severe AD dementia	0.64 (0.32)	Belger *et al*. 2022[163]
Spouse Caregiver - Community Setting		
MCI due to AD	0.82 (0.18)	Data on file, 2023[162]
Mild AD dementia	0.72 (0.25)	Data on file, 2023[162]
Moderate AD dementia	0.54 (0.34)	Data on file, 2023[162]
Severe AD dementia	0.38 (0.30)	Adjusted, Belger *et al*. 2022[163]
Spouse Caregiver – Residential Care Setting		
MCI due to AD	0.82 (0.18)	Assumed same as community setting
Mild AD dementia	0.72 (0.25)	Assumed same as community setting
Moderate AD dementia	0.71 (0.25)	Belger *et al*. 2022[163]
Severe AD dementia	0.64 (0.32)	Belger *et al*. 2022[163]

Abbreviations: AD: Alzheimer's disease; EQ-5D: EuroQol 5 dimensions; MCI: mild cognitive impairment; SD: standard deviation; UK: United Kingdom.

B.3.4 *Cost and healthcare resource use identification, measurement and valuation*

Healthcare resource use and cost inputs were based on clinical trial data and published literature as well as standard publicly available databases. Inflation adjustments were applied for any costs from before 2022 according to the Consumer Prices Index including owner occupiers' housing costs (CPIH).[158]

The following cost and resource use categories were captured in the analysis:

- Drug acquisition, administration and background therapy costs (B.3.4.1)
- Background therapy costs (B.3.4.1)
- Diagnostic and monitoring costs (for both amyloid clearance and AEs) (B.3.4.2)
- Medical management of the condition by health state, including residential care costs (B.3.4.3)
- AEs (B.3.4.4)

As described in Section B.3.1.3, the perspective on costs is that of the UK NHS and PSS and therefore included only costs that would be incurred by the NHS and PSS.

B.3.4.1 Intervention and comparators' costs and resource use

Drug acquisition costs

Drug acquisition costs for donanemab were provided by Eli Lilly and are presented in Table 33.

Table 33: Donanemab drug acquisition costs (PAS)

Treatment	Pack/vial cost	Pack/vial size	Strength	mg per pack/vial	Cost per mg (PAS)
Donanemab	[redacted]	20.0 ml	17.5 mg/ml	350.00 mg	[redacted]

In order to accurately estimate drug costs, the model considered the appropriate treatment duration lengths, mode of administration, dosing intervals, titration, and discontinuation.

In the model, the relative dose intensity (RDI) for donanemab was adjusted to account for a proportion of patients for whom treatment was interrupted due to ARIA with duration of treatment interruption as observed from the TRAILBLAZER-ALZ 2 trial. The RDI is intended to represent the ratio between the dose effectively administered and the target dose. An overall RDI of 95.14% was applied for donanemab, calculated as a weighted average based on the following inputs: the proportion of patient for whom treatment was interrupted due to ARIA (36.8%), the mean duration of treatment interruption as observed from the TRAILBLAZEER-ALZ 2 trial (72.4 days) and the trial duration (18 months or 19.55 28-day dosing cycles, informed by TRAILBLAZER-ALZ 2 data.

Dosing inputs for donanemab are presented in Table 34.

Table 34: Donanemab dosing inputs

Start	End	Dosing Frequency	Dosage	Dose Method	RDI
Treatment start	3 months	Q4W	700 mg	Fixed dose	95.14%
3 months	12 months	Q4W	1,400 mg	Fixed dose	95.14%
12 months	18 months	Q4W	1,400 mg	Fixed dose	95.14%

Abbreviations: Q4W: every 4 weeks; RDI: relative dose intensity.

Drug administration costs

Donanemab is administered via intravenous infusion (IV) which is associated with administration costs. The administration costs considered within the model are summarised in Table 35.

Duration of treatment administration was based on 30 minutes of treatment administration followed by 30 minutes of observation based on the TRAILBLAZER-ALZ 2 trial.[5] For the base-case, unit costs were from the NHS costs [154](£256.95; cost inclusive of subsequent observation; currency code SB13Z).

Table 35: Administration costs

Treatment	Route of administration	Administration duration	Cost of administration	Frequency of administration
Donanemab	IV	1.0 hour[a]	£207.59	Q4W

Treatment	Route of administration	Administration duration	Cost of administration	Frequency of administration
Established clinical management	No administration costs were included in the model for BSC			

Footnotes: [a]Assumes 30 minutes administration followed by 30 minutes observation based on the TRAILBLAZER-ALZ 2 protocol.
Abbreviations: IV: intravenous.

Background therapy costs

Costs of background therapy (i.e., concomitant medications, including memantine and AChEIs) were also included in the model. The annual cost of each medication, and the proportion of patients who receive each medication by AD stage are specified in Table 36 below.

Table 36: Costs and distribution for concomitant medications

Medication	Annual Cost	Proportion of patients who receive the medication by AD stage (%)				Source
		MCI due to AD	Mild AD dementia	Moderate AD dementia	Severe AD dementia	
Acetylcholinesterase inhibitor	£8.61[a]	[redacted]	[redacted]	[redacted]	[redacted]	Lilly Data on File: Adelphi DSP 2024[142]
Memantine	£12.52[b]	[redacted]	[redacted]	[redacted]	[redacted]	

[a] Patients are assumed to receive 10 mg daily over the course of a year based on the dosing schedule reported on the BNF. [b] Patients are assumed to receive 20 mg daily over the course of a year based on the dosing schedule reported on the BNF.
Abbreviations: AD: Alzheimer's disease; MCI: mild cognitive impairment.

B.3.4.2 Diagnostic and monitoring costs

Costs associated with diagnostic testing, amyloid monitoring and adverse events monitoring were applied in the model. The unit costs of each resource category was extracted from the NHS and are summarised in Table 37 below.[154]

Table 37: Unit costs for diagnostics and monitoring resources

Imaging/testing unit costs	Unit costs	Source
MRI scan	£197.34	NHS Costs – Year 2021/22[154]; Currency code – RD01A
Amyloid PET scan	[redacted]	-
Amyloid PET procedure only	£607.85	NHS Costs – Year 2021/22[154]; Currency code – RN01A
Tracer	[redacted]	Assumption based on a draft price for an amyloid radiotracer in the UK
Blood-based biomarkers*	£43.81	NHS Costs – Year 2021/22[154]; Currency code – DAPS02
CSF	£406.00	NHS Costs – Year 2021/22[154]; Currency code – HC72A
APOE ε4 test	£43.81	NHS Costs – Year 2021/22[154]; Currency code – DAPS02

*Blood-based biomarkers are not yet available in the UK an as such, this cost is an assumption based on the currency code for 'direct access pathology services: histopathology and histology'.
Abbreviations: APOE: apolipoprotein E; CSF: cerebrospinal fluid; MRI: magnetic resonance imaging; PET: positron emission tomography.

Diagnostic testing costs

In the base case, it was assumed that all patients entering the model are Aβ positive, as Aβ positivity is a requirement for receiving amyloid-targeting therapies. As amyloid testing is not currently a routine part of NHS clinical practice, the cost of testing and identifying patients eligible for treatment with donanemab was included in the model. Prior to initiating treatment, in addition to amyloid testing, all patients are required to have received a recent MRI (within one year) and also to be tested for APOE ε4 status.

Diagnostic tests included in the model were APOE ε4 testing, MRI scanning, and CSF testing and PET scanning for amyloid detection (Table 38).

Table 38: Diagnostic testing descriptions and resource use

Test	Description	Base case resource use
CSF	Amyloid detection	90%*
Amyloid PET scan	Amyloid detection	10%*
MRI scan	MRI conducted before treatment to check patient meets eligibility criteria	75%
APoE ε4 test	Genetic test to identify carriers of the APOE ε4 gene	100%
Blood-based biomarker test	*Potential use as screening test*	*Only included in scenario analysis*

Abbreviations: APOE: apolipoprotein E; ARIA: amyloid-related imaging abnormalities; CSF: cerebrospinal fluid; MRI: magnetic resonance imaging; PET: positron emission tomography.
*A factor of 2 is applied to these proportions to account for patients who receive a diagnostic test but do not go on to receive treatment with donanemab

A weighted cost was estimated based on the specified use mix and unit costs for each type of diagnostic testing, and was applied in model cycle 1. In the model, it is assumed that all patients are APoE-4 tested (100%), 90% are tested via CSF for amyloid positivity, and 10% via a PET scan for amyloid positivity. It is assumed that 75% patients receive baseline MRI scans, as 25% are assumed to have already received an MRI scan within last 12 months within current practice; this is in line with the anticipated label for donanemab which states that a baseline MRI is only required for those who had not received an MRI in the previous 12 months.[185] The proportion of PET scans and CSF tests are increased by a factor of 2 to account for the cost of testing for patients who will not go on to receive treatment. This multiplier is further explored in scenario analysis.

As described in B.1.3.1, it is anticipated that blood-based biomarker tests could be used for diagnostic testing in the future. Introducing blood-based biomarkers into the diagnostic pathway may improve efficiency and cost effectiveness of identifying and treating patients with amyloid positivity. Therefore, scenario analyses were conducted to investigate the impact of introducing blood-based biomarker testing as a rule-out test ahead of PET/CSF testing or as a rule-in test, and are described in further detail in Section B.3.10.3.

Amyloid monitoring costs

Costs of monitoring amyloid positivity during treatment (only for those modelled to follow a treat-to-clear regimen) were based on costs for an amyloid PET scan. These costs were applied in the model based on the proportion of patients screened for amyloid positivity at baseline, and at 6 months and 12 months. In the model base case, these costs are applied for 10% of patients (100% of which were screened for amyloid positivity at baseline) and for these patients on treatment at 6 and 12 months as per the TRAILBLAZER-ALZ 2 trial protocol and trial duration.[5] Unit costs for amyloid monitoring resources are summarised in Table 37.

Adverse event monitoring costs

Monitoring costs for adverse events were applied as a one-time cost in the first model cycle and were based on the total frequency of MRI scans for ARIA event monitoring over the trial period specified. As per the SmPC for donanemab, it was assumed that patients would receive three regular MRI scans during the follow-up period; prior to the second dose, prior to dose increase and prior to the seventh dose.[185] In addition, the cost of two additional ad-hoc MRI scans was assumed when symptomatic ARIA occurred.

B.3.4.3 Health-state unit costs and resource use

Healthcare resource utilisation costs by AD severity and setting (community/residential care) were specified in the model for the following cost categories: NHS costs (patient health care costs, caregiver health care costs), and residential care costs (excluding patient out-of-pocket costs). As discussed in Section B.1.3, most costs in AD dementia are expected to increase with AD severity as the patients' burden increases. In order to inform costs per AD dementia stage, cost inputs were evaluated based on UK-based AD dementia models identified in the SLR (Appendix E) as well as additional sources identified through a targeted literature review.

For the base-case, annual costs of residential care were estimated based on a per-week resident fee of £1,442 for residential care obtained from Jones *et al*. PSSRU report.[186] The per-week fee includes capital costs, local authority expenditure, external services (nursing, GP), and personal expense allowance. In the model, of the total estimated annual costs for residential care, 49.65% were categorised under direct medical costs as these were covered under the NHS perspective based on NICE guidance, and the remaining were categorised under direct non-medical. This proportion is aligned to estimates by Age UK and NG71.[187, 188]

As the above studies did not report costs for MCI due to AD, costs for MCI were sourced from Luppa 2008,[189] a prospective cohort study investigating resource use and costs associated with MCI due to AD based in Germany (costs were converted to British pounds). For the remaining health states in the community setting, costs were taken from the PSSRU report, which is a recognised UK source of health and social care costs. This is the only available source which reports total costs of health and social care by dementia stage, aligning with the NHS and PSS perspective outlined in NICE's reference case. These costs were originally derived by Pennington *et al.* (2016), based on data from 69 memory assessment services in the UK recruiting 25 patients each.[190] Resource use data were collected from patient's carers at baseline, 3-months, and 6-months including health and social care components and were comprehensively micro costed based on PSSRU (2014) and NHS Reference Costs (2014) to generate total costs per dementia stage. As the PSSRU report does not report costs for the MCI due to AD health state, these have been sourced from Wittenberg *et al*. (2019) and are assumed to be equal to mild dementia (no dependency).[93]

Table 39 presents the healthcare resource utilisation costs considered in the base case.

Table 39: Health resource utilisation annual costs (base case)

Health states	Total HRU costs *(covered by NHS/PSS)*
Community	
MCI due to AD*	£1,385.75**
Mild AD dementia	£20,392.00***
Moderate AD dementia	£23,851.00***
Severe AD dementia	£44,941.00***
Residential Care	
All health states	£37,332.00

Footnotes: *As the PSSRU report does not report costs for the MCI health state, these have been sourced from Wittenberg *et al.* (2019) and are assumed to be equal to mild dementia (no dependency). **This cost was inflated using the CPIH index.[158] ***Includes health and social care costs.
Abbreviations: AD: Alzheimer's disease; HRU: health resource utilisation; MCI: mild cognitive impairment; NHS: National Health Service.
Source: PSSRU Report.[186] Wittenberg *et al.* (2019)[93]

To investigate the impact of these cost assumptions on the cost-effectiveness results, an alternate source of healthcare resource utilisation costs was explored within a scenario analysis. Costs sourced from Wittenberg *et al.* (2019) inflated to 2022 prices, are presented in Table 40.[93]

Table 40: Health resource utilisation annual costs (scenario analysis)

Health states	Total HRU costs *(covered by NHS/PSS)*
Community	
MCI due to AD**	£1,475.45
Mild AD dementia	£9,911.18
Moderate AD dementia	£15,331.85
Severe AD dementia	£20,271.40

Footnotes: *Includes health and social care costs.** As Wittenberg *et al.* (2019) do not report costs for the MCI health state, these are assumed to be equal to mild dementia (no dependency)
Abbreviations: AD: Alzheimer's disease; HRU: health resource utilisation; MCI: mild cognitive impairment; NHS: National Health Service.
Source: Wittenberg *et al.* (2019)[93].

To investigate the impact of including informal care costs on the cost-effectiveness results, an costs of informal care were explored within a non-reference case scenario analysis, as invited within Issue 8 of the NICE HTA Lab report. Costs sourced from Wittenberg *et al.* (2019) inflated to 2022 prices, are presented in Table 41.[93]

Table 41: Informal care annual costs (scenario analysis)

Health states	Total informal care costs *(Non-reference case analysis)*
Community	
MCI due to AD	£12,380.95
Mild AD dementia	£17,929.93
Moderate AD dementia	£26,654.33

Severe AD dementia	£34,256.10

Abbreviations: AD: Alzheimer's disease; MCI: mild cognitive impairment.
Source: Wittenberg *et al.* (2019)[93].

Terminal care costs

A one-off terminal care cost of £7,274.00 was applied within the model.[186]

B.3.4.4 Adverse reaction unit costs and resource use

The incidence of AEs – ARIA events, IRRs, hypersensitivity and anaphylactic reaction – are discussed in Section B.3.2.4. In the model, the ARIA cost was assumed equivalent to two MRI scans and was not differentiated by type of ARIA event. This is a conservative assumption as in practice, only one MRI may be required per patient. Unit costs for MRI scans were sourced from the NHS.[154]

For anaphylaxis, costs were based on a weighted average of emergency department visits (VB01Z:VB09Z).[154] IRRs and hypersensitivity were micro costed based on the resource use recommended by treatment guidelines. Cost estimation for IRRs and hypersensitivity assumed a single dose of cetirizine 10mg.

The costs of treating AEs were multiplied by the probabilities of each event to derive the total cost for each treatment. ARIA event costs (including MRI scan costs) were calculated as a six-month period cost to align with the model cycle length and were applied in the first model cycle (6 months) to align with the occurrence of ARIA events described in Section B.3.2.4. Other AE costs were calculated as six-month period costs to align with the model cycle length and were applied for the duration of the trial period, adjusting for the proportion of each model cycle (6 months).

Table 42: AE management costs

Adverse event	Cost	Source
ARIA event	£410.62	Assumes 2 MRIs with 1.8% of patients also requiring an emergency department visit (NHS 2021/22: VB01Z)[154]
Infusion related reactions	£49.37	NHS 2021/2022[154]; Difference between simple and more complex parenteral chemotherapy at first attendance (SB12Z and SB13Z) plus the cost of cetirizine
Hypersensitivity	£49.37	Assumed equal to infusion related reactions
Anaphylactic reaction	£309.86	NHS 2021/2022[154]; Weighted average of Consultant-Led Emergency Medicine Costs VB01Z : VB09Z

Abbreviations: ARIA: amyloid-related imaging abnormalities.

B.3.4.5 Miscellaneous unit costs and resource use

No additional costs were considered in the base case of the economic model.

B.3.5 *Severity*

As noted in Section B.1.3, AD is a severe, progressive neurodegenerative disease that has a huge impact on an individual's life. Based on the results of a QALY shortfall analysis,

summarised in Table 43, Table 44 and Table 45 below, donanemab meets the criteria for a severity modifier. Proportional shortfall was calculated as ~86.95%, which is above the 85% threshold for a 1.2× severity multiplier. In line with the reference case and the perspective relevant to this appraisal, both patient and caregiver QALYs were included in the calculation of proportional shortfall. Both patients and caregivers can be considered to be people living with the condition.

Table 43: Summary features of QALY shortfall analysis

Factor	Value		Relevant section in submission
	MCI due to AD	Mild AD dementia	
Proportion female (%)	49.60%	57.00%	Section B.3.2.1
Starting age (years)	72.81	72.76	Section B.3.2.1

Abbreviations: QALY: quality adjusted- life year.

Table 44:Summary of health state benefits and utility values for QALY shortfall analysis

Health state	Utility value: mean	Undiscounted life years
MCI due to AD	Patient: 0.76 Child Caregiver: 0.84 Spouse Caregiver: 0.82	Patient (Community): 0.52 Patient (Residential): 0.00 Carer QALY Loss: 0.00
Mild AD	Patient: 0.74 Child Caregiver: 0.775 Spouse Caregiver: 0.715	Patient (Community): 1.92 Patient (Residential): 0.04 Carer QALY Loss: −0.26
Moderate AD	Patient: 0.59 Child Caregiver (Community): 0.615 Child Caregiver (Residential Care): 0.71 Spouse Caregiver (Community): 0.542 Spouse Caregiver (Residential Care): 0.71	Patient (Community): 1.32 Patient (Residential): 0.10 Carer QALY Loss: −0.58
Severe AD	Patient: 0.36 Child Caregiver (Community): 0.455 Child Caregiver (Residential Care): 0.64 Spouse Caregiver (Community): 0.382 Spouse Caregiver (Residential Care): 0.64	Patient (Community): 2.67 Patient (Residential): 1.16 Carer QALY Loss: −2.19

Abbreviations: AD: Alzheimer's Disease; MCI: mild cognitive impairment; QALY: quality adjusted- life year.

Table 45: Summary of QALY shortfall analysis[191]

Scenario	Expected total QALYs for the general population (discounted	Total QALYs that people living with a condition would be expected to have with current treatment (discounted)	QALY shortfall	
			Absolute	Proportional
Reference case: MVH value set + HSE 2014 ALDVMM model (Hernandez Alava et al)	8.04	1.05	6.99	86.95%
Alternative A: 5L to 3L mapping (Hernandez	7.96	1.05	6.91	86.81%

Alava et al) + HSE 2017-2018				
Alternative B: 5L to 3L mapping (van Hout et al) + HSE 2017-2018	8.00	1.05	6.95	86.88%
Alternative C: MVH value set + health state profiles	7.91	1.05	6.86	86.73%
Alternative D: MVH value set + HSE 2012+14	8.06	1.05	7.01	86.97%

Abbreviations: QALY: quality adjusted- life year.

B.3.6 *Uncertainty*

As demonstrated by the results presented in B.3.9, donanemab has the potential to represent a cost-effective use of resource versus BSC. However, Lilly acknowledge that areas of uncertainty may remain in the cost-effectiveness analysis due to the limited long-term efficacy and safety data, and uncertainty in healthcare cost and resource use. The following are the key areas of uncertainty:

- Clinical trials conducted in AD are often of a limited duration despite the long duration of disease. As such it is difficult to capture long-term evidence on the efficacy and safety of donanemab meaning there is uncertainty around long-term clinical effects of the drug
- There are limited UK data reporting comprehensive costs associated with care for patients with AD by disease state especially those considering a perspective which aligns with NICE's reference case (NHS and PSS perspective), meaning there is uncertainty around these costs within the model
- Given that there are currently no treatment options for patient with MCI due to AD, there are limited incentives to diagnose these patients and it is expected that MCI due to AD is currently underdiagnosed. There is therefore uncertainty in treatment demand, i.e., the number of eligible patients, referral rates and the true number of patients that will initiate amyloid-targeting therapies

B.3.7 *Managed access proposal*

Given the novel and innovative nature of donanemab, it may be a candidate for a recommendation through managed access. As discussed in Section B.3.6, Lilly acknowledge that areas of uncertainty may remain in the cost-effectiveness analysis due to the limited long-term efficacy and safety data, uncertainty in healthcare cost and resource use, and uncertainty in terms of the cost of service expansion required to deliver amyloid-targeting therapies.

However, further data are anticipated to become available during any managed access agreement timeframe, which should provide sufficient evidence for reducing uncertainty in those key areas. Specifically:

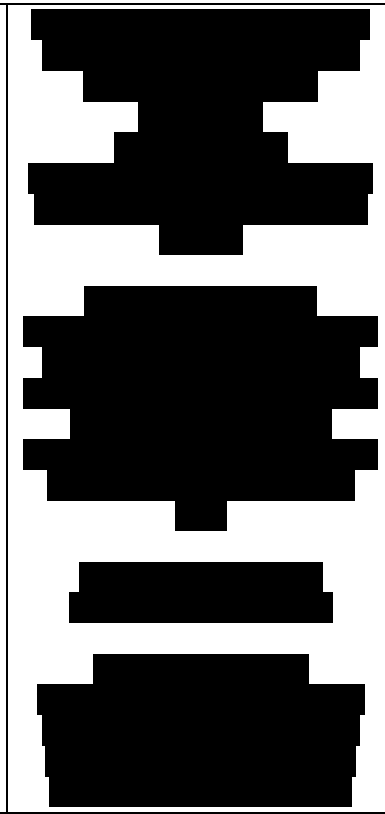
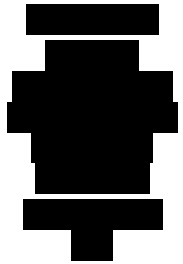
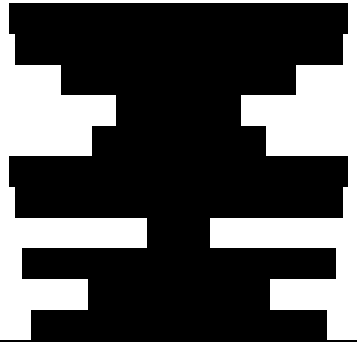
- Data from the long-term extension of the pivotal TRAILBLAZER-ALZ 2 trial are anticipated to become available in Q4 2024 which will provide evidence beyond 18-months for patients who have completed treatment on donanemab and continue to be followed up

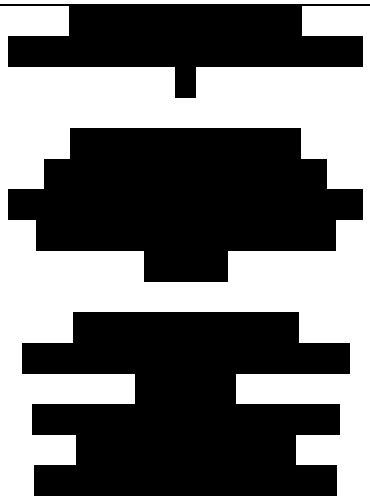
- TRAILBLAZER-ALZ 5: An international multi-country trial of donanemab in early symptomatic AD, collecting clinical outcomes, biomarker outcomes, and quality of life information
- TRAILBLAZER-ALZ 6: A study of different donanemab dosing regimens in adults with early Alzheimer's Disease and the impact on ARIA-E. Outcomes on ARIA-H and biomarker information will also be collected
- Comparative long-term effectiveness studies are to be carried out in US and Europe, which will provide long-term real-world evidence of patients treated with donanemab compared with a matched placebo cohort
- A real-world evidence study in is planned for 2024 and is anticipated to complete in Q4 2024. The study will generate evidence on resource use in both health and social care provision for patients with MCI due to AD and patients with AD dementia over time, based on integrated UK datasets
- A real-world evidence study is planned for the period 2024 – 2026, with annual data read-outs describing the patient diagnostic and disease management profile within the UK, inclusive of the use of biomarkers for diagnosis
- Lilly are also exploring additional sources of data collection for resolving key areas of uncertainty. Should donanemab receive a recommendation through managed access, the above sources and any further data collection that is initiated would be used to inform the evidence base for the cost-effectiveness analysis in the resubmission to NICE

Table 46: Planned studies and how they will address uncertainty in the model

Study	Primary Endpoint Summary	Key Secondary Endpoint	Duration of Follow Up	Anticipated Date of Availability	UK Sites / Participants	Category of Uncertainty Addressed
TB-ALZ EXT (AACH)	**Evaluate safety and tolerability of open label donanemab** in patients who received placebo in an originating-donanemab trial **(Part B)**	[redacted]	Up to 36 months	[redacted]	No	Long-term clinical uncertainty Long-term safety
TB-4 (AACN)	**Co-Primary:** To assess the superiority of donanemab versus aducanumab on complete brain amyloid plaque clearance at 6 months - Overall population - Low Medium Tau population	Superiority of donanemab versus aducanumab on degree of brain amyloid plaque reduction at 6,12,18 months Superiority of donanemab versus aducanumab in time to reach complete amyloid plaque clearance. Non-inferiority donanemab versus aducanumab on degree of brain amyloid plaque reduction after 6M donanemab vs 12M aducanumab; after 6M donanemab vs 18M aducanumab	18 months	Q2 2024	No	Confirm rates of amyloid clearance over time
TB-5 (AACO)	Assess rate of clinical progression (cognitive and/or functional decline) as measured by iADRS score in:	**Change from baseline through Week 76** in at least 1 of - the low-medium tau pathology population or	18 months	[redacted]	Yes estimated 200 patients	Confirm clinical utility and safety

	- low-medium tau pathology at baseline and	- the overall population (combined population) as measured by CDR-SB; ADAS-Cog13 score; ADCS-iADL score; MMSE score **Change in brain amyloid deposition** **Assess safety and tolerability of donanemab** **Evaluate the quality of life, dependency level, healthcare resource utilization,** as measured by QoL-AD, dependency level (derived from ADCS-ADL), RUD-Lite, and NPI				
TB-6 (AACQ)	Assess the effect of alternative donanemab dosing regimens versus the standard donanemab dosing regimen on ARIA-E frequency - Proportion of participants with any occurrence of ARIA-E by **Week 24**	Assess effect of alternative donanemab dosing regimens on ARIA-E frequency at Week 52 Assess the effect of alternative donanemab dosing regimens versus standard donanemab dosing regimen on brain amyloid deposition at 24,52 & 76 weeks Assess effect of alternative dosing regimens on ARIA-H frequency and any ARIA E or ARIA H by severity at week 24,52,76 weeks Assess peripheral PK and presence of anti-donanemab antibodies	76 weeks	Q4 2025	Yes: 6 sites (Bristol, Winchester, London, Birmingham, Plymouth)	Optimization of risk/benefit

TB-REAL OUS (AACR)	To compare the effect of donanemab and Usual Care versus Usual Care alone on dependence level in participants with early symptomatic AD PET Sub-study To determine the proportion of participants who reach amyloid clearance To assess amyloid reduction rates and change in amyloid over time.					Long-term clinical uncertainty; confirm clinical meaningfulness Long-term safety, Resource Use
TB-REAL US (AACS)	To compare the effect of donanemab plus usual care versus usual care alone on dependence level in participants with early symptomatic AD					Long-term clinical uncertainty; confirm clinical meaningfulness Long-term safety

						
UK Real World Evidence Studies	Generate evidence to inform resource use in health and social care for patients with MCI due to AD and AD dementia	Patient characteristics, diagnostic experience, and treatment journey in patients with MCI due to AD and AD dementia	Retrospective	Q4 2024 – Q4 2026	Not applicable	Cost and resource use in health and social care

Abbreviations: AD: Alzheimer's disease; ADAS-Cog13: 13-Item Alzheimer's Disease Assessment Scale – Cognitive Subscale; ARIA: amyloid-related imaging abnormality; CDR-SB: Summary of Boxes of the Clinical Dementia Rating Scale; EXT: extension; iADRS: Integrated Alzheimer's Disease Rating Scale; MMSE: Mini-Mental State Exam; QoL-AD: quality of life: Alzheimer's Disease; TB-ALZ: TRAILBLAZER-ALZ trials.

B.3.8 *Summary of base-case analysis inputs and assumptions*

B.3.8.1 Summary of base-case analysis inputs

A summary of inputs for the base case analysis is presented in Table 47.

Table 47: Summary of variables applied in the economic model

Variable	Value	Measurement of uncertainty (distribution)	Reference to section in submission
Model settings			
Discount rate (costs)	3.5%	-	Section B.3.1.3
Discount rate (benefits)	3.5%	-	Section B.3.1.3
Time horizon	Lifetime	N/A	Section B.3.1.3
Baseline population - proportion MCI due to AD severity at initiation	20.37%	Beta	Section B.3.2.1
Percent Male - MCI due to AD Severity at Initiation	50.40%	Beta	Section B.3.2.1
Percent male - mild AD dementia severity at initiation	43.00%	Beta	Section B.3.2.1
Population age - MCI due to AD severity at initiation	72.81	Normal	Section B.3.2.1
Population age - mild AD dementia severity at initiation	72.76	Normal	Section B.3.2.1
Caregiver characteristics			
Mean age of child caregivers	54.1	Normal	Section B.3.2.1
Number of caregivers per patient	1.8	Normal	Section B.3.2.1
Proportion of child caregivers	29.14%	Beta	Section B.3.2.1
Disease progression			
Natural progression of disease	Multivariate	Dirichlet (Multivariate Beta)	Section B.3.2.3
Annual probabilities of institutionalisation by disease stage			
MCI due to AD	0.00%	Beta	Section B.3.2.3
Mild AD dementia	1.20%	Beta	Section B.3.2.3
Moderate AD dementia	3.40%	Beta	Section B.3.2.3
Severe AD dementia	6.60%	Beta	Section B.3.2.3
HR vs BSC on CDR-SB Scale			
HR vs BSC on CDR-SB scale for donanemab - MCI due to AD	0.62	Lognormal	Section B.3.2.2
HR vs BSC on CDR-SB scale for donanemab - mild AD dementia	0.62	Lognormal	Section B.3.2.2
HR vs BSC on CDR-SB scale for donanemab - moderate AD dementia	0.62	Lognormal	Section B.3.2.2
HR vs BSC on CDR-SB scale for BSC - MCI due to AD	1.00	Lognormal	Section B.3.2.2

HR vs BSC on CDR-SB scale for BSC - Mild AD dementia	1.00	Lognormal	Section B.3.2.2
HR vs BSC on CDR-SB scale for BSC - moderate AD dementia	1.00	Lognormal	Section B.3.2.2
Treatment discontinuation			
Treatment discontinuation due to amyloid clearance	0.00%	0.00%	Section B.3.2.2
Proportion stopping treatment for donanemab at 6 months	29.70%	Beta	Section B.3.2.2
Proportion stopping treatment for donanemab at 12 months	36.42%	Beta	Section B.3.2.2
Treatment discontinuation for positive stopping rules - start of treatment effect waning			
Donanemab	10 Cycles	Gamma	Section B.3.2.2
BSC	0 Cycles	Gamma	Section B.3.2.2
Treatment discontinuation for negative stopping rules - % that discontinue after 6 months and do not reinitiate			
Donanemab	13.10%	Beta	Section B.3.2.2
BSC	0.00%	Beta	Section B.3.2.2
Treatment discontinuation for adverse events - start of treatment effect waning			
Donanemab	2 Cycles	Gamma	Section B.3.2.2
BSC	0 Cycles	Gamma	Section B.3.2.2
Treatment discontinuation for adverse events - duration Tx effect post-discontinuation			
Donanemab	5 Cycles	Gamma	Section B.3.2.2
BSC	0 Cycles	Gamma	Section B.3.2.2
Treatment discontinuation for adverse events - % of full treatment effect retained			
Donanemab	0.00%	Beta	Section B.3.2.2
BSC	0.00%	Beta	Section B.3.2.2
% Patients screened for amyloid clearance			
Percent of patients screened for amyloid clearance - donanemab	10.00%	Beta	Section B.3.2.2
Percent of patients screened for amyloid clearance - BSC	0.00%	Beta	Section B.3.2.2
Relative dose intensity			
RDI for donanemab	95.14%	Gamma	Section B.3.4.1
Administration costs by method			
Infusion: 1st hour	£207.59	Gamma	Section B.3.4.1
Concomitant medications			
Annual cost of acetylcholinesterase inhibitor	£8.60	Gamma	Section B.3.4.1
Annual cost of memantine	£12.52	Gamma	Section B.3.4.1
Use of acetylcholinesterase inhibitor for MCI due to AD	[redacted]	Beta	Section B.3.4.1
Use of acetylcholinesterase inhibitor for Mild AD Dementia	[redacted]	Beta	Section B.3.4.1
Use of acetylcholinesterase inhibitor for Moderate AD Dementia	[redacted]	Beta	Section B.3.4.1

Use of acetylcholinesterase inhibitor for Severe AD Dementia	[redacted]	Beta	Section B.3.4.1
Use of memantine for MCI due to AD	[redacted]	Beta	Section B.3.4.1
Use of memantine for mild AD Dementia	[redacted]	Beta	Section B.3.4.1
Use of memantine for Moderate AD Dementia	[redacted]	Beta	Section B.3.4.1
Use of memantine for Severe AD Dementia	[redacted]	Beta	Section B.3.4.1
Resource utilisation costs			
Imaging/testing unit costs			
Unit cost for MRI scan	£197.34	Gamma	Section B.3.4.2
Unit cost for amyloid PET scan	[redacted]	Gamma	Section B.3.4.2
Unit cost for blood-based biomarkers	£43.81	Gamma	Section B.3.4.2
Unit cost for CSF	£405.78	Gamma	Section B.3.4.2
Unit cost for APOE ε4 test	£43.81	Gamma	Section B.3.4.2
Adverse events monitoring			
# Units used for ARIA events monitoring for donanemab	3.00	Normal	
# Units used for ARIA events monitoring for BSC	0.00	Normal	
Direct medical annual costs - community			
Patient health care costs - MCI due to AD	£1,385.75	Gamma	Section B.3.4.3
Patient health care costs - Mild AD Dementia	£20,392.00	Gamma	Section B.3.4.3
Patient health care costs - moderate AD dementia	£23,851.00	Gamma	Section B.3.4.3
Patient health care costs - severe AD dementia	£44,941.00	Gamma	Section B.3.4.3
Direct medical annual costs - institutionalised			
Patient health care costs	£37,332.00	Gamma	Section B.3.4.3
Terminal care cost			
Terminal care cost	£7,274.00	Gamma	Section B.3.4.3
Distribution of diagnostic testing resources			
Donanemab - MRI Scan	75.00%	Beta	Section B.3.4.2
Donanemab - Amyloid PET Scan	20.00%	Beta	Section B.3.4.2
Donanemab - Blood-Based Biomarkers	0.00%	Beta	Section B.3.4.2
Donanemab - CSF	180.00%	Beta	Section B.3.4.2
Donanemab - APOE ε4 Test	100.00%	Beta	Section B.3.4.2
BSC - MRI Scan	0.00%	Beta	Section B.3.4.2
BSC - Amyloid PET Scan	0.00%	Beta	Section B.3.4.2
BSC - Blood-Based Biomarkers	0.00%	Beta	Section B.3.4.2
BSC - CSF	0.00%	Beta	Section B.3.4.2

BSC - APOE ε4 Test	0.00%	Beta	Section B.3.4.2
Adverse events			
Incidence rate of all-grade ARIA events and serious AEs (Grade 3+) over trial period			
Donanemab - ARIA Event	36.80%	Beta	Section B.3.2.4
BSC - ARIA Event	0.00%	Beta	Section B.3.2.4
Distribution of ARIA-E events			
% Symptomatic ARIA-E for Donanemab	25.37%	Beta	Section B.3.2.4
% Symptomatic ARIA-E for BSC	0.00%	Beta	Section B.3.2.4
Adverse event costs			
Cost for ARIA event	£410.62	Gamma	Section B.3.4.4
Cost for infusion related reactions	£49.37	Gamma	Section B.3.4.4
Cost for hypersensitivity	£49.37	Gamma	Section B.3.4.4
Cost for anaphylactic reaction	£309.86	Gamma	Section B.3.4.4
Utility			
Patient baseline health state utility - community			
MCI due to AD	0.76	Beta	Section B.3.3.5
Mild AD Dementia	0.74	Beta	Section B.3.3.5
Moderate AD Dementia	0.59	Beta	Section B.3.3.5
Severe AD Dementia	0.36	Beta	Section B.3.3.5
Patient baseline health state utility – residential care			
MCI due to AD	0.76	Beta	Section B.3.3.5
Mild AD Dementia	0.74	Beta	Section B.3.3.5
Moderate AD Dementia	0.59	Beta	Section B.3.3.5
Severe AD Dementia	0.36	Beta	Section B.3.3.5
Patient age (utility source – Landeiro et al. [2020])[146]			
Patient age	78.40	Normal	Section B.3.3.5
Child caregivers baseline utility			
Child caregivers baseline utility - community - MCI due to AD	0.84	Beta	Section B.3.3.5
Child caregivers baseline utility - community - Mild AD Dementia	0.78	Beta	Section B.3.3.5
Child caregivers baseline utility - community - Moderate AD Dementia	0.62	Beta	Section B.3.3.5
Child caregivers baseline utility - community - Severe AD Dementia	0.46	Beta	Section B.3.3.5
Child caregivers baseline utility – residential care - MCI due to AD	0.84	Beta	Section B.3.3.5
Child caregivers baseline utility - residential care - Mild AD Dementia	0.78	Beta	Section B.3.3.5
Child caregivers baseline utility - residential care - moderate AD Dementia	0.71	Beta	Section B.3.3.5

Child caregivers baseline utility - residential care - severe AD Dementia	0.64	Beta	Section B.3.3.5
Child caregivers age in source	54.10	Normal	Section B.3.3.5
Child caregivers male % in source	25.40%	Beta	Section B.3.3.5
Spouse caregivers baseline utility			
Spouse caregivers baseline utility - community - MCI due to AD	0.82	Beta	Section B.3.3.5
Spouse caregivers baseline utility - community - mild AD Dementia	0.72	Beta	Section B.3.3.5
Spouse caregivers baseline utility - community - moderate AD Dementia	0.54	Beta	Section B.3.3.5
Spouse caregivers baseline utility - community - severe AD Dementia	0.38	Beta	Section B.3.3.5
Spouse caregivers baseline utility - residential care - MCI due to AD	0.82	Beta	Section B.3.3.5
Spouse caregivers baseline utility - residential care - mild AD Dementia	0.72	Beta	Section B.3.3.5
Spouse caregivers baseline utility - residential care - moderate AD Dementia	0.71	Beta	Section B.3.3.5
Spouse caregivers baseline utility - residential care - severe AD Dementia	0.64	Beta	Section B.3.3.5
Spouse caregivers age in source	73.40	Normal	Section B.3.3.5
Spouse caregivers male % in source	41.20%	Beta	Section B.3.3.5
AE disutilities			
ARIA event	−0.14	Lognormal	Section B.3.3.4
Anaphylactic reaction	−0.12	Lognormal	Section B.3.3.4
AE duration			
ARIA event	72.4	Normal	Section B.3.3.4
Anaphylactic reaction	30	Normal	Section B.3.3.4
Mortality	0	0	Section B.3.3.4
Treatment-related mortality in Cycle 1			
Treatment-related mortality in cycle 1 for donanemab	0.35%	Lognormal	Section B.3.2.5
Treatment-related mortality in cycle 1 for BSC	0.00%	Lognormal	Section B.3.2.5
Mortality HR: community Setting vs General Population			
Mortality HR: community setting vs general population for MCI due to AD	1.00	Lognormal	Section B.3.2.5
Mortality HR: community setting vs general population for AD Dementia	2.55	Lognormal	Section B.3.2.5
Hazard Ratio Residential Care vs Community Setting			
Mortality HR: Residential Care vs Community Setting	1.00	Lognormal	Section B.3.2.5

Abbreviations: AD: Alzheimer's disease; AE: adverse event; APOE: apolipoprotein E genotype; ARIA: amyloid-related imaging abnormality; BSC: best supportive care; CDR-SB: Clinical Dementia Rating Sum of Boxes; CSF: cerebrospinal fluid; HR: hazard ratio; MCI: mild cognitive impairment; PET: positron emission tomography; RDI: relative dose intensity.

B.3.8.2 Assumptions

A list of the key assumptions used in the base case analysis is provided in Table 48 below.

Table 48: Key base case assumptions

Parameter	Assumption	Justification	Addressed in scenario analysis
Population	Patients can enter the model in either MCI due to AD or mild AD dementia stage	To align with the target patient population for donanemab in the TRAILBLAZER-ALZ 2 trial	The effect of varying the proportion of patients entering the model in the MCI due to AD or mild AD dementia is investigated within scenario analyses.
Model transitions	In each cycle, patients can stay in the current state or progress to a more severe state.	Backward transitions as shown in some analysis of RWE (e.g., Potashman *et al*. 2021, Spackman *et al*. 2012) may be possible due to scale noise, but they are unlikely to occur based on the underlying disease pathology.[175, 176] This was controlled for within the NACC analysis that forms the base case.	n/a
Modelling of amyloid diagnosis	Patients undergo a diagnostic process before entering the model, but only costs are considered (screening failure considered only as additional costs)	Model reflects only the costs for different options of confirming biomarker status. Patients entering the model were all assumed to be diagnosed as amyloid positive. The treatment effect sourced from the trial accounts for the chance of inclusion of any false positive diagnoses in the trial.	The effect of varying the distribution of diagnostic testing resources is investigated within scenario analyses.
Treatment stopping rules	• Patients can receive donanemab according to a fixed dose duration for 18 months or treat-to-clear for up to a maximum of 18 months (in a ratio of 90%:10%) • Patients will stop receiving donanemab if they progress to severe AD dementia health state before completing amyloid clearance or 18 months treatment duration • Patients will not be initiated when already in residential care but will continue treatment when moving into residential care • Patients can discontinue treatment due to AEs	• This assumption is based on the treatment stopping rules detailing in the anticipated label and anticipated PET scanner capacity • There is a lack of evidence to support the assumption that patients will continue donanemab in the severe AD dementia health state and the TRAILBLAZER-ALZ trials were not designed to evaluate treatment effect in patients with severe AD dementia. Additionally, during the 18-month treatment duration, it is considered unlikely that people will progress into the severe AD dementia health state	The effect of varying the percentage of patients receiving donanemab on a fixed-dose duration or treat-to-clear is investigated within scenario analyses.

		• This assumption is considered clinically appropriate. Additionally, the percentage of patients that moved into residential care over the first three cycles of the model was negligible (<2%) • This is in line with data collected during the TRAILBLAZER-ALZ 2 trial	
Treatment effect assumptions	• For patients who discontinue treatment due to positive stopping rules (fixed treatment duration and/or discontinuation due to amyloid clearance), treatment effect will be maintained for 5 years before treatment waning starts • For patients who discontinue due to AEs (stop permanently), treatment effect will be continued for the remainder of the 12 months after which is it is waned • For patients who discontinue due to progression to severe AD dementia, no treatment effect is retained, and the patient follows natural disease progression	Justification for these assumptions is provided in Section B.3.2.2.	Treatment waning assumptions are investigated within scenario analyses
Residential Care	Patients who are in residential care are assumed to remain so until death or the end of the time horizon.	Patients within the residential care setting are unlikely to return to the community setting due to underlying disease pathology.	n/a
Mortality	No increased risk of mortality is assumed in MCI due to AD and increased risk of death versus general population is applied to patients in AD dementia health states.	Patients with AD dementia have an increased risk of death versus the general population, based on ONS data	The effect of varying the source of additional mortality risk data is investigated within scenario analyses.

Abbreviations: AD: Alzheimer's disease; AE: adverse event; HR: hazard ratio; MCI: mild cognitive impairment; ONS: office for national statistics.

B.3.9 *Base-case results*

B.3.9.1 Base-case incremental cost-effectiveness analysis results

The base case deterministic and probabilistic cost-effectiveness results for donanemab versus established clinical management are presented in Table 49 and Table 50, respectively. In the probabilistic analyses, donanemab was found to be cost-effective compared to BSC at a willingness to pay (WTP) threshold of £20,000 per QALY, yielding an ICER of £16,203.38. Similar results were found in the deterministic analyses where donanemab was associated with an ICER of £16,447.16 when compared to BSC.

The clinical outcomes and disaggregated base case cost-effectiveness results (by cost category, including health states) and QALYs (by health state) are presented in Appendix E.

Table 49: Deterministic base-case results

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)
Donanemab	[redacted]	7.75	2.11				
BSC	[redacted]	7.73	1.26	£13,953.18	0.02	0.85	£16,447.16

Abbreviations: ICER: incremental cost-effectiveness ratio; LYG: life years gained; QALY: quality-adjusted life year.

Table 50: Probabilistic base-case results

Technologies; mean (95% CI)	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)
Donanemab	[redacted]	7.77 (7.16 – 8.42)	2.21 (1.04 – 3.35)				
BSC	[redacted]	7.75 (7.12 – 8.40)	1.36 (0.17 – 2.57)	£13,726.17 (4,333 – 21,780)	0.02 (-0.01 – 0.06)	0.85 (0.52 – 1.20)	£16,203.38 (4,015 – 38,982)

Abbreviations: BSC: best supportive care; ICER: incremental cost-effectiveness ratio; LYG: life years gained; QALY: quality-adjusted life year.

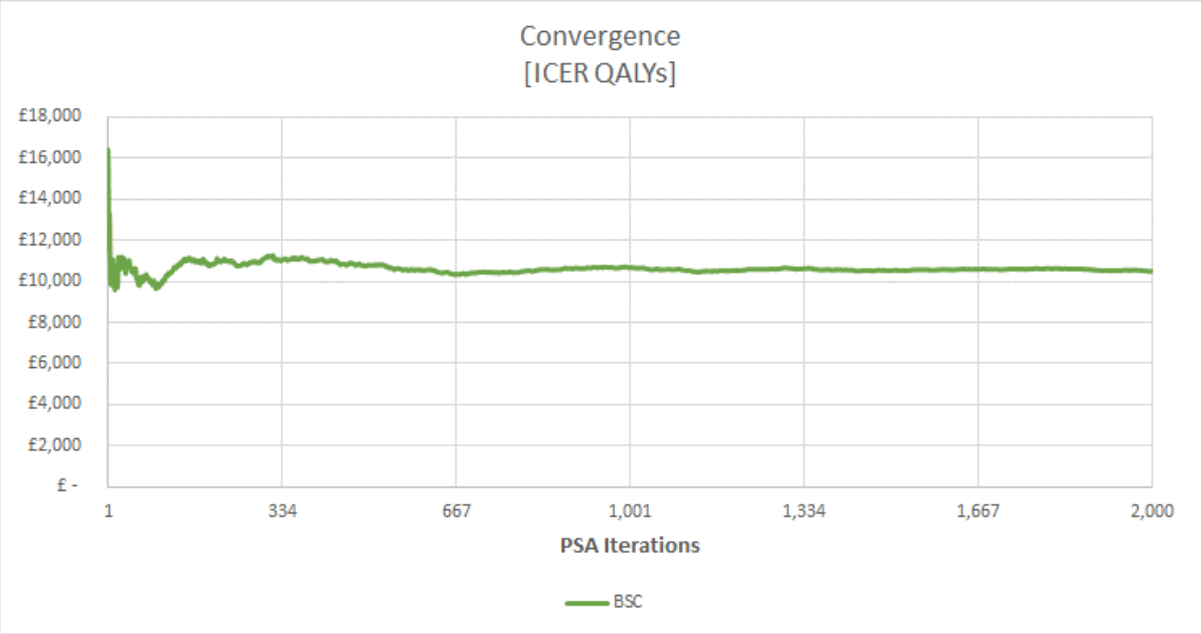
B.3.10 *Exploring uncertainty*

Parameter uncertainty in the model was assessed via both probabilistic and deterministic sensitivity analyses the results of which are presented in Sections B.3.10.1 and B.3.10.2, respectively. In addition, key assumptions in the model were explored in several probabilistic scenario analyses, the results of which are presented in Section B.3.10.3. Overall, it is considered that all relevant uncertainties included in the analyses have been adequately accounted for and the base case results were found to be robust to uncertainty in the key model inputs and assumptions.

B.3.10.1 Probabilistic sensitivity analysis

Probabilistic sensitivity analyses (PSA) were run with 2,000 iterations, with estimates of model parameters based on the uncertainty in the source data (where data availability permitted). Uncertainties in parameter values were estimated including for clinical inputs, costs and utility values. Measurement of uncertainties was captured by 95% CIs or standard errors (SEs) for each parameter. In the absence of CIs or SEs from published sources, the SE for the parameter was assumed to be 10% of the mean value. An ICER convergence plot is provided in Figure 20 below.

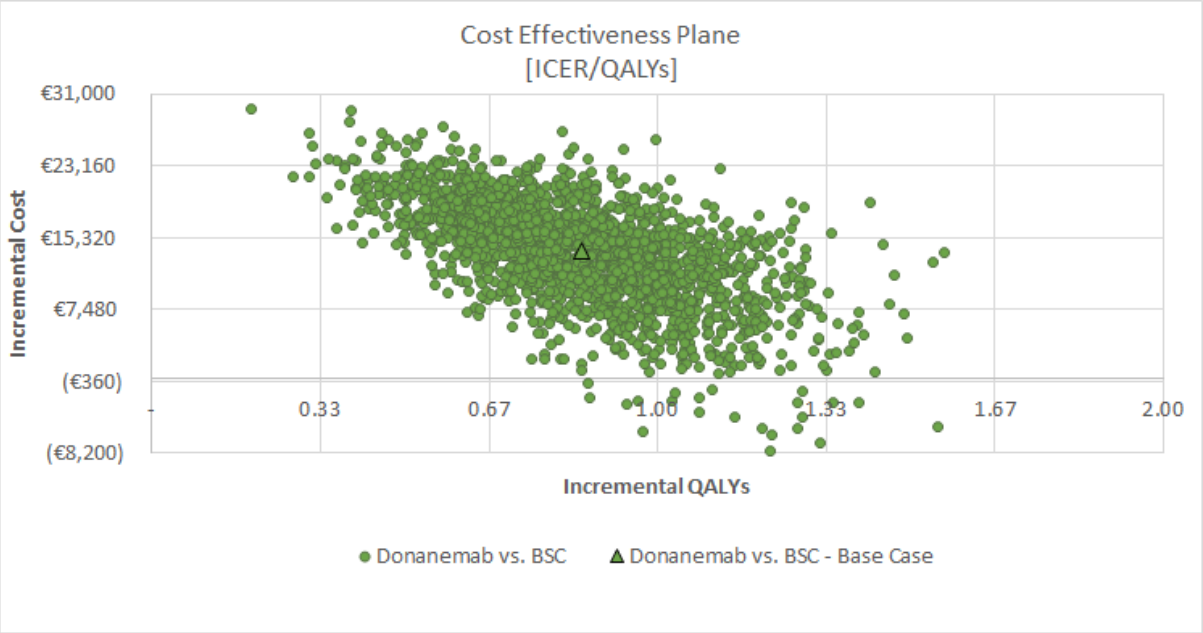
Figure 20: ICER convergence plot



*The convergence plot is calculated using the undiscounted results.
Abbreviations: ICER: incremental cost-effectiveness ratio.

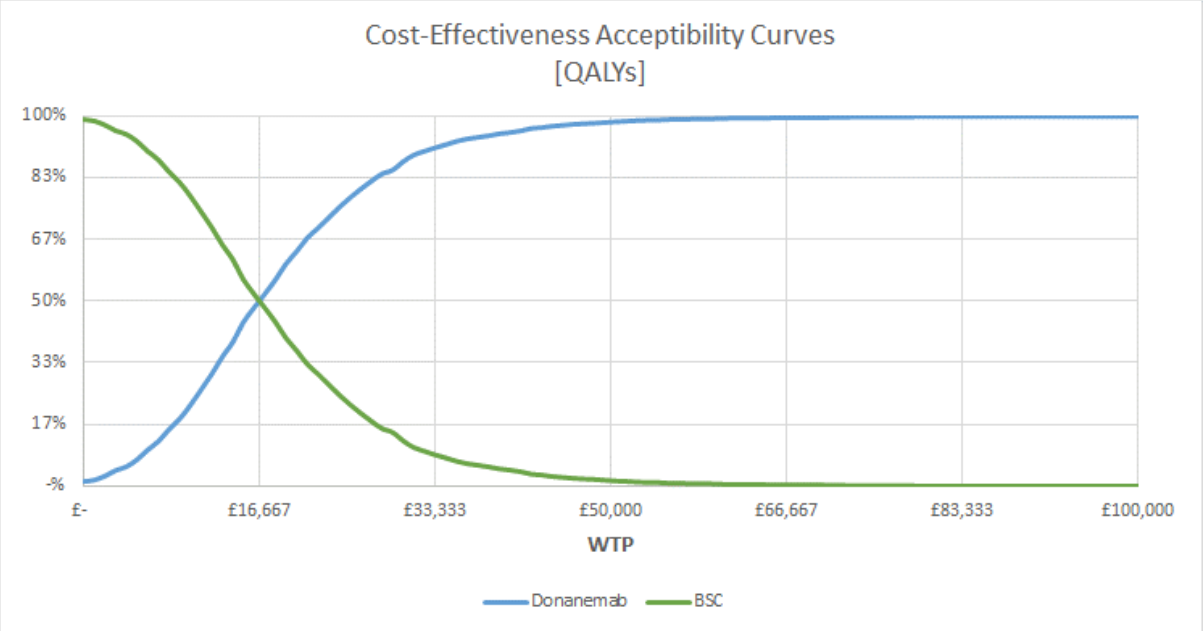
The probabilistic cost-effectiveness planes for donanemab versus BSC is presented in Figure 21. The cost-effectiveness acceptability curve is presented in Figure 22. The PSA found the probability of donanemab being cost-effective to be 63% and 87% at a WTP threshold of £20,000 and £30,000 per QALY, respectively.

Figure 21: Probabilistic cost-effectiveness plane



Abbreviations: BSC: best supportive care; ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year.

Figure 22: Cost-effectiveness acceptability curve

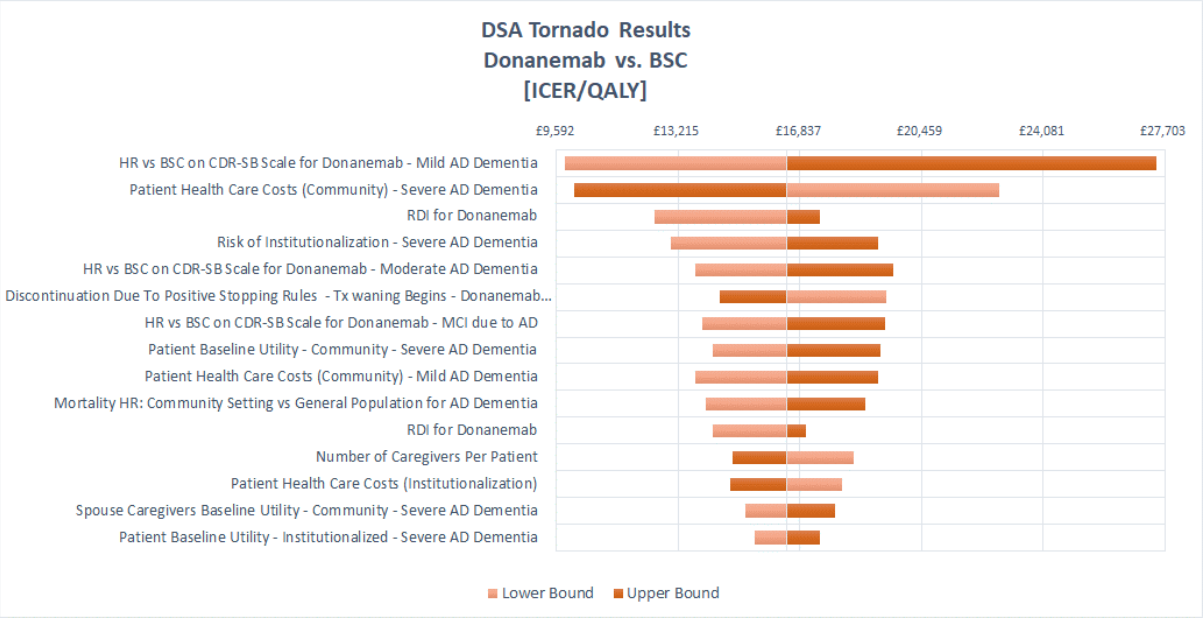


Abbreviations: BSC: best supportive care; QALY: quality-adjusted life year; WTP: willingness to pay.

B.3.10.2 Deterministic sensitivity analysis

In order to assess the robustness of the base case cost-effectiveness results, deterministic sensitivity analyses (DSA) were conducted. The tornado diagrams for donanemab versus BSC is presented in Figure 23. The top 15 most influential parameters on the base case are presented in each case. The three most influential parameters in the model were the treatment effect versus BSC in mild AD dementia patients, the direct health and social care costs in severe AD dementia patients, and the relative dose intensity applied to donanemab treatment.

Figure 23: DSA tornado diagram for donanemab versus BSC



*RDI for donanemab appears twice in the tornado diagram, as separate inputs are programmed in the model corresponding with different treatment periods.
Abbreviations: AD: Alzheimer's disease; BSC: best supportive care; CDR-SB: Clinical Dementia Rating Sum of Boxes; DSA: deterministic sensitivity analysis; HR: hazard ratio; ICER: incremental cost-effectiveness ratio; QALY: quality adjusted life-year; RDI: relative dose intensity.

B.3.10.3 Scenario analysis

Several scenario analyses were conducted to assess the impact of the uncertainty associated with key inputs and assumptions in the economic model. A summary of the scenario analysis results for donanemab versus relevant comparators are presented in Table 51.

Discount rate

- Base case: a discount rate of 3.5% was applied for both costs and effects in the model
    - Scenario: a discount rate of 1.5% was applied for both costs and effects in the model

Proportion of patients starting in MCI due to AD and mild dementia due to AD health states

- Base case: the proportion of patients starting in the MCI due to AD and mild dementia due to AD health states in the model is informed by the proportion of MCI due to AD and mild dementia due to AD patients in the TB2 trial
    - Scenario: all patients start the model in the MCI due to AD health state
    - Scenario: all patients start the model in the mild dementia due to AD health state

Proportion of patients following a fixed duration of donanemab treatment and a treat-to-clear strategy with monitoring for amyloid clearance at 6-months and 12-months

- Base case: The proportion of patients following a treat-to-clear strategy (10%) is informed by clinical opinion on PET scanner and tracer capacity in the UK, with the remaining proportion of patients being treated for a fixed duration of 18-months
    - Scenario: all patients are treated for a fixed duration of 18-months

- Scenario: all patients follow treat-to-clear strategy

Number of amyloid diagnostic tests (PET and CSF) required to identify one eligible patient

- Base case: It was assumed that two amyloid diagnostic tests would be required to identify one eligible patient, and the total cost of all diagnostic tests are included
    - Scenario: four diagnostic tests required to identify one eligible patient
    - Scenario: one diagnostic test required to identify one eligible patient, with additional cost of blood-based biomarker screening test included to represent a 'rule-out' blood-based biomarker test in future
    - Scenario: 'Rule-in' blood-based biomarker test becomes available, which negates requirement for confirmatory PET / CSF scan

Modelling of natural history of disease progression

- Base case: natural history was informed by the NACC (CDR-SB) analysis
    - Scenario: natural history was informed by the Postashman (CDR-SB) analysis [175]

Caregiver utilities

- Base case: Caregiver utilities were informed by two vignette studies. The caregiver utility study conducted in 2023 included the MCI, mild and moderate health state. The severe health state was derived from a study conducted in 2016 and the utility value for the severe health state was adjusted for the observed difference in the moderate health state between the old and new study to account for the time difference in which external factors may impact the general population's level of QoL. [162] [163]
    - Scenario: No adjustment for the severe health state was performed.

Modelling of treatment effect of donanemab

- Base case: Full treatment effect of donanemab is applied for 10 model cycles (which represents 18m of treatment and 3.5yrs of treatment effect beyond discontinuation) based on reaccumulation of amyloid-levels to 24.1CL (defined as positive in the trial). A gradual linear waning effect is then applied over a further 10 cycles (5 years)
    - Scenario: Consider amyloid positivity threshold from Clarity-AD (30CL)[192]
    - Scenario: Limit long-term waning period to 3-years
    - Scenario: extending the long-term treatment waning period in patients who discontinue donanemab due to AE over a period of 5 years
    - Scenario: reducing the long-term treatment waning period in patients who discontinue donanemab due to AE over a period of 6 months
    - Scenario: reducing long-term treatment waning period in patients received a full course of treatment to 2.5 years
    - Scenario: extending the long-term treatment waning period in patients received a full course of treatment to 7.5 years

Mortality

- Base case: mortality was informed by ONS data

- Scenario: mortality was informed by the Liang *et al.* (2021) meta-analysis[193]

Health-state costs

- Base case: health state resource utilisation costs sourced from the PSSRU Report.[186] and Wittenberg et al. (2018) [92]
    - Scenario: health state resource utilisation costs based on Dementia UK Report[92] for all health states

Perspective on costs

- Base case: NHS / PSS perspective
    - Scenario: include informal care costs based on Dementia UK Report[92], invited as a non-reference case analysis within Issue 8 of the NICE HTA Lab report

The results of all probabilistic scenario analyses were comfortably under the £30,000 willingness-to-pay threshold, with the vast majority being below the lower end of the threshold range usually considered by NICE. This demonstrates that the cost-effectiveness results of donanemab versus established clinical management without donanemab for patients with MCI due to AD and Mild AD dementia are robust to uncertainty around key inputs.

Table 51: Scenario analysis results for donanemab versus BSC

Scenario	Description	Incremental Costs (£)	Incremental QALYs	ICER (£/QALY)
Base Case		£13,726.17	0.85	£16,203.38
1	Discount rate of 1.5%	£12,057.28	0.94	£12,834.30
2	100% patients enter model in MCI due to AD	£6,768.11	1.04	£6,487.14
3	100% patients enter model in mild dementia due to AD	£15,461.56	0.80	£19,380.08
4	Fixed-duration of treatment only	£14,088.00	0.85	£16,560.60
5	Treat-to-clear only	£12,333.05	0.85	£14,548.02
6	4 diagnostic tests required to identify one eligible patient	£14,782.24	0.85	£17,437.07
7	Blood-based biomarker test becomes available (rule-out)	£13,187.50	0.85	£15,555.93
8	Blood-based biomarker test becomes available (rule-in)	£12,640.65	0.85	£14,910.86
9	Transition probabilities (Potashman *et al*)	£13,028.15	0.85	£15,412.03
10	Caregiver utility values (unadjusted)	£13,690.22	0.74	£18,536.38
11	Treatment effect waning (medium-term) based on amyloid positivity level of 30cL	£12,039.92	0.92	£13,100.64

12	Patients who discontinue due to AE wane treatment over 10 cycles	£13,521.88	0.87	£15,569.24
13	Patients who discontinue due to AE wane treatment over 1 cycle	£14,325.78	0.82	£17,475.41
14	Treatment waning effect applied over 5 cycles (patients who did not discontinue due to AE)	£15,125.76	0.79	£19,160.73
15	Treatment waning effect applied over 15 cycles (patients who did not discontinue due to AE)	£12,764.08	0.89	£14,417.60
16	Mortality based on meta-analysis	£15,291.41	0.78	£19,556.84
17	Direct Health and Social Care Costs (Wittenberg et al. 2019)	£21,906.69	0.85	£25,841.04
18	Informal care costs included (Wittenberg et al. 2019)	£7,760.35	0.84	£9,223.21

Abbreviations: ICER: incremental cost-effectiveness analysis; QALY: quality adjusted life year.

B.3.11 *Subgroup analysis*

N/A - no subgroups were considered relevant to this appraisal and as such no subgroup analyses were included in the cost-effectiveness analysis.

B.3.12 *Benefits not captured in the QALY calculation*

AD is a complex disease with a widespread burden to both patients and caregivers that may not be fully captured by the QALY calculation, including the following factors:[194]

- Patients typically becomes dependent on the caregiver for their everyday functioning, which makes the burden on the caregiver an essential aspect of the disease.
- The value of a new technology for patients works to reduce the fear of AD.
- The availability of a disease-modifying therapy could also have far-reaching implications and is likely to lead to the evolution of clinical care pathways in the NHS that will in turn, lead to overall improvements in the care provided for all patients with dementia.

B.3.13 *Validation*

B.3.13.1 Validation of cost-effectiveness analysis

Internal validity

A technical model validation was conducted to evaluate the validity of the model programming and sources used to derive input parameters in the model adaptation. A technical validation

examines the extent to which mathematical calculations in the model are performed correctly and evaluates their consistency with the model's specifications. The following steps were undertaken to ensure the model's technical validity:

- **Extreme-value testing**: each model parameter was set to extremely low and high values to identify any inconsistencies in model behaviour or unexpected results.
- **Technical review**: the model programming was reviewed by a senior modeller who was not part of the project team. The technical review process included using different model settings to ensure that they yielded expected calculations. The validator also checked the links between worksheets to ensure that the correct cells were referenced. In addition, mathematical formulae and the sequence of calculations for each parameter and the model engine were checked.
- **Input verification**: values for all parameters were reviewed against source documents, and the inconsistencies were corrected.

Following the validation process, errors identified by the validator were corrected, and the revised model was rechecked by the validator.

External validity

Additional reviews were performed by clinical and HTA experts (external to the team that developed the model), and evaluated the base-case inputs, structural assumptions and the validity of results. Based on the recommendations shared by the experts, inputs and assumptions were updated to align with clinical practice and HTA guidelines. Programming changes were undertaken to align structural assumptions with clinical practice and accommodate additional scenario analyses. All programming changes were internally validated as described above.

B.3.14 *Interpretation and conclusions of economic evidence*

Summary of the cost-effectiveness evidence

In order to assess the cost-effectiveness of donanemab versus BSC in patients with either MCI due to AD or mild AD dementia and evidence of amyloid beta pathology, a *de novo* cost-effectiveness analysis was conducted from the perspective of the NHS and PSS in England.

In the base case analysis donanemab was found to be cost-effective compared to established clinical management at a WTP of £30,000 per QALY and thus donanemab can be considered a cost-effective use of NHS resources in the treatment of AD. The probabilistic ICER for donanemab versus established clinical management was £16,203.38.

The PSA found the probability of donanemab being cost-effective to be 63% and 87% at a WTP threshold of £20,000 and £30,000 per QALY, respectively. The DSA results identified that the three most influential parameters in the model were the treatment effect versus BSC in mild AD dementia patients, the direct health and social care costs in severe AD dementia patients, and the relative dose intensity applied to donanemab treatment. Scenario analyses conducted to address sources of uncertainty in the model showed that the results of all scenario analyses were comfortably under the £30,000 willingness-to-pay threshold, with the vast majority being below the lower end of the threshold range usually considered by NICE. This demonstrates that the cost-effectiveness results of donanemab versus established clinical management without

donanemab for patients with MCI due to AD and Mild AD dementia are robust to uncertainty around key inputs.

Strengths and limitations

The key evidence base for this submission is the TRAILBLAZER-ALZ 2 trial, which was a randomised, double-blind, placebo-controlled study which demonstrated that donanemab was consistently associated with slowing AD clinical progression across all cognitive and functional endpoints tested, regardless of statistical model used. As the trial allowed supportive care and non-disease modifying therapies to be taken alongside either donanemab or placebo, the placebo arm of the TRAILBLAZER-ALZ 2 trial can be considered an appropriate proxy for the comparator of relevance, BSC.

One challenge in modelling AD is the data limited data on longer-term treatment effect of donanemab as well as on how amyloid clearance is connected to the re-accumulation process. The connection between ARIA events, discontinuation due to ARIA events, and magnitude of treatment effect after discontinuation are also a source of uncertainty. This is because amyloid clearance can be correlated with the probability of having an ARIA event, and therefore patients who discontinue due to an ARIA event may also experience faster amyloid clearance and a stronger treatment effect. To mitigate this challenge, a data-collection plan has been proposed (as detailed in Section B.3.7).

Finally, the economic model presented was built to align with the NICE reference case, adopting an NHS and PSS perspective, a time horizon sufficient to capture fully all costs and QALY gains associated with the donanemab and the relevant comparator (BSC), and discount rates for costs and benefits of 3.5%. The economic model is designed to consider all relevant health states for AD. A range of sensitivity analyses were conducted that demonstrate that the cost-effectiveness results were robust to an extensive number of scenario analyses.

Conclusions

In summary, donanemab represents an important treatment option for patients with AD and will help to address the high unmet need experienced by patients with MCI due to AD and mild AD dementia and allow patients to spend longer in less severe stages of the disease. Donanemab represents a cost-effective use of NHS resources versus the available BSC options in England; sensitivity analyses showed that the ICERs calculated are robust to changes in the modelling parameters. The availability of a disease-modifying therapy could also potentially have far-reaching implications and is likely to lead to the evolution of clinical care pathways in the NHS that will in turn, lead to overall improvements in the care provided for all patients with dementia. Donanemab is therefore a valuable new addition to the clinical pathway of care for AD.

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B.5 Appendices

Appendix A

Appendix B

Appendix C

Appendix D

Appendix E

Appendix F

Appendix G

Appendix H

Appendix I

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Donanemab for treating mild cognitive impairment or mild dementia caused by Alzheimer's disease [ID6222]

EAG Report Issue 4 – Additional Analyses

June 2024

File name	Version	Contains confidential information	Date
ID6222 EAR Issue 4 Additional Analyses_3rd June 2024 [CON]	Final	Yes	3rd June 2024

Key Issue 4: Risk of bias associated with the TRAILBLAZER-ALZ trials and the potential impact on the measurement of the treatment effect

The EAG stated that additional evidence may help resolve this issue:

> "*We would like the company to provide sensitivity analyses of the hazard ratio, using a Cox proportional hazard model, of disease progression over time to week 76 as measured by the CDR-SB in which participants who experience ARIA or infusion-related reactions or both are censored after the first occurrence (if they have not already experienced disease progression), for both the TRAILBLAZER-ALZ and TRAILBLAZER-ALZ 2 trials. We would also like the company to provide economic model scenario analyses using the hazard ratios for the treatment effect when these participants are censored. It would be desirable if the company also conducted the same sensitivity analyses of the hazard ratios with censoring of these participants when the iADRS is used to measure disease progression.*"

These analyses have been carried out in the TRAILBLAZER-ALZ 2 population in line with the original analysis and are provided alongside this response. The analyses were the same as the original ones planned a priori in the SAP, with the additional specification that participants were censored at their first occurrence of ARIA or infusion related reaction (IRR) if they had not already experienced disease progression. Hazard ratios are similar to the corresponding original analyses. In the updated analyses, the number of events drops (due to the additional censoring) in a higher proportion in the donanemab arm than in the placebo arm; however, given that the additional censorings occur early in the treatment period the impact on the result is limited.

Table 1. Comparison of HR Results (Original Analyses vs. Censored for ARIA / IRR)

Analysis	Hazard Ratio	95% CI		Source
CDR-SB				
Original Analysis	0.623	0.519	0.748	Eli Lilly. Data on File.
Censored ARIA/IRR	[redacted]	[redacted]	[redacted]	Eli Lilly. Data on File.
iADRS				
Original Analysis	0.7	0.582	0.842	Eli Lilly. Data on File.
Censored ARIA/IRR	[redacted]	[redacted]	[redacted]	Eli Lilly. Data on File.

Due to the similarity in the results, updated economic model results are not provided as they are not expected to meaningfully change.

Note that participants who experienced an ARIA event or IRR after the 1st visit, where a clinical worsening occurred, but before the 2nd consecutive visit were considered as having had an event and were not censored.

References

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Donanemab for treating mild cognitive impairment or mild dementia caused by Alzheimer's disease [ID6222]

Summary of Information for Patients (SIP)

13th March 2024

File name	Version	Contains confidential information	Date
ID6222_Eli Lilly_Donanemab_SIP [NoCON]_13Mar24	2	No	13th March 2024

Summary of Information for Patients (SIP):

The pharmaceutical company perspective

What is the SIP?

The Summary of Information for Patients (SIP) is written by the company who is seeking approval from NICE for their treatment to be sold to the NHS for use in England. It is a plain English summary of their submission written for patients participating in the evaluation. It is not independently checked, although members of the public involvement team at NICE will have read it to double-check for marketing and promotional content before it is sent to you.

The **Summary of Information for Patients** template has been adapted for use at NICE from the Health Technology Assessment International – Patient & Citizens Involvement Group (HTAi PCIG). Information about the development is available in an open-access IJTAHC journal article

SECTION 1: Submission summary

1a) Name of the medicine (generic and brand name):

Generic name: Donanemab
Brand name: *Not yet publicly available, please refer to* **Section B.1.2 in Document B**

1b) Population this treatment will be used by:

Please outline the main patient population that is being appraised by NICE:

The population that this treatment will be used for is adult patients with either **mild cognitive impairment (MCI)** or **mild dementia** due to Alzheimer's disease (AD), and evidence of **amyloid beta pathology** confirmed by a validated diagnostic test (as described in **Section 2b**).

1c) Authorisation:

Please provide marketing authorisation information, date of approval and link to the regulatory agency approval. If the marketing authorisation is pending, please state this, and reference the section of the company submission with the anticipated dates for approval.

The **Medicines and Healthcare products Regulatory Agency** (**MRHA**) is reviewing whether donanemab should be approved and granted **marketing authorisation** as a treatment for adults with MCI due to AD or mild AD dementia. The marketing authorisation

for donanemab is therefore pending. More information on this can be found in **Document B** in **Section B.1.2**.

Please note:
Further explanations for the words and phrases highlighted in **black bold text** are provided in the glossary (**Section 4b**). These are only highlighted the first time they are used, so please check the glossary when needed. Cross-references to other sections are all highlighted in **green**.

1d) Disclosures.

Please be transparent about any existing collaborations (or broader conflicts of interest) between the pharmaceutical company and patient groups relevant to the medicine. Please outline the reason and purpose for the engagement/activity and any financial support provided:

The table below shows support from Eli Lilly to relevant patient advocacy groups in the United Kingdom (UK), and how the company engages or supports these charities and/or patients who use them.

Patient Organisation	Project	Financial Support
ARUK	Representative from ARUK to participate in an international multi-stakeholder working group with the purpose of providing input and feedback to Lilly on company strategy and environment shaping initiatives for Alzheimer's disease. May 2023 – Jan 2024	No payment other than reimbursement of reasonable expenses incurred to attend the meeting.
	Collaborative project centred on the optimisation of early Alzheimer's Disease Care Pathways using real world data and insights gathered from the front line of care	No payment

SECTION 2: Current landscape

2a) The condition – clinical presentation and impact

Please provide a few sentences to describe the condition that is being assessed by NICE and the number of people who are currently living with this condition in England.

Please outline in general terms how the condition affects the quality of life of patients and their families/caregivers. Please highlight any mortality/morbidity data relating to the condition if available. If the company is making a case for the impact of the treatment on carers this should be clearly stated and explained.

The main condition that donanemab is planned to treat is Alzheimer's disease (AD).

What is Alzheimer's disease?

AD is a disease which affects a person's brain.[1] Over time the damage in the brain causes dementia,[1] a general term for problems with memory, thinking and behaviour.[2] AD is the most common cause of dementia.[1] AD is not a normal part of ageing, but the chances of getting the disease increases as we get older.[2, 3] In normal ageing the brain naturally changes and our thought processes slow down. But, in AD, a **protein** called **amyloid** builds-up in the brain, followed by a protein called **tau**,[4] and these cause damage to cells.[3] This process affects how the brain works.[3] As such, the presence of amyloid plaques early in AD increases the likelihood of disease progression.[5]

What are the signs and symptoms of Alzheimer's disease?

AD affects different people in different ways. Some common symptoms include memory problems, thinking and reasoning difficulties, problems with language and speaking, confusion, mood and behaviour changes, and disorientation.[1, 6] AD and its symptoms gets worse over time and a person with AD will need more support with everyday tasks and living.[1]

What causes Alzheimer's disease?

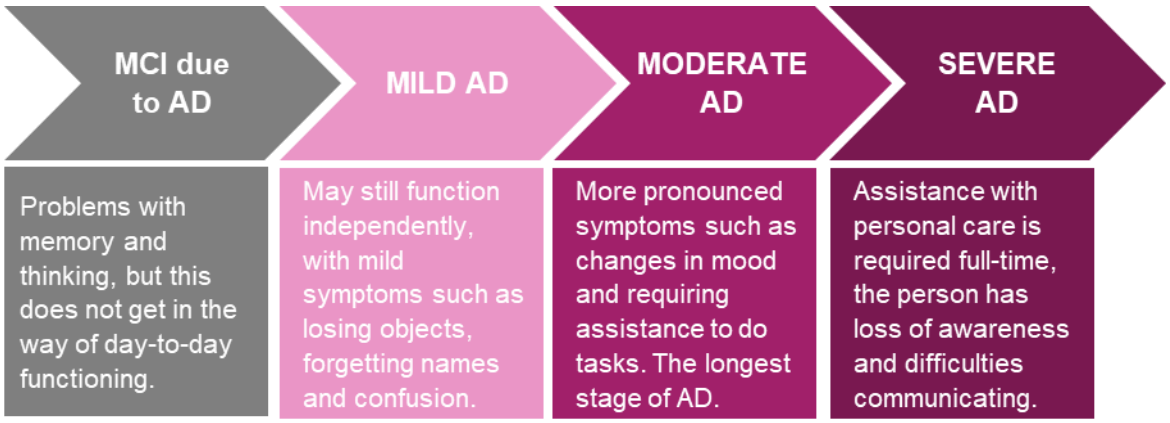
The causes of the disease are very complex and are not yet fully understood.[3] However, we do know that the build-up of two proteins, amyloid and then tau, in the brain causes damage to cells and makes it harder for the brain to work properly.[1] When amyloid builds up it forms **plaques** in the spaces between nerve cells.[2] Tau builds up inside cells and its fibres twist into **tangles**.[2] These protein structures play an important role in the development of AD.

How does Alzheimer's disease progress over time?

Changes in the brain related to AD happen many years before symptoms are noticeable.[7-9] Some common early symptoms may appear before a diagnosis of dementia.[10] Often this is referred to as MCI.[10] People with MCI have mild symptoms but are still able to do everyday activities.[11] Not all people with MCI will go on to develop AD or other types of dementia.[10, 12]

After MCI, there are three main stages of AD: mild AD (early stage), moderate AD (middle stage) and severe AD (late stage). **Figure 1** gives a simple summary of the stages, but these will vary from person to person.

Figure 1: Stages of AD[13]



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

How many people get Alzheimer's disease?

In 2021, there were around 944,000 people living with dementia in the UK.[14] As the population of the UK is getting older, the number of people with dementia is increasing.[15] AD is the most common cause of dementia with about 50–75% of dementia cases being because of AD in the UK.[3, 16, 17] The number of people diagnosed with mild dementia due to AD in the UK has been estimated to be around 80,000.[17-19]

Alzheimer's disease risk factors[20]

Age

Age is the biggest risk factor for AD. Above 65, a person's risk of developing AD doubles about every five years. Although most people with AD are over 65, younger people can also get young-onset AD.

Sex

There are more women over the age of 65 with AD than men. This is mostly because women live longer than men. However, women over 80 have a slightly higher risk than men their age of getting AD.

Genes

Some **genes** increase a person's risk of getting AD. The most important risk gene is apolipoprotein E (APOE). Certain versions of the APOE gene can make a person up to four times more likely to develop Alzheimer's.

What is the impact of Alzheimer's disease (disease burden)?

Emotional impact

As AD affects functions like memory and thinking, it becomes more difficult to make decisions, engage in activities and socialise. This can make a person with AD feel lonely and isolated and can have a dramatic effect on a person's **quality of life**.[21] People with AD can feel scared and ashamed, and sometimes this stops them from getting medical help.[22] Depression and anxiety are common with dementia, and can start to develop in the early stages of the disease.[23] Changes in mood and disorientation also affect people with

AD.[23] Together, these can have a very big impact on a person's life, health and relationships.

Later in the disease, people with AD need full-time care.[24] This is because they can become vulnerable, and it can be unsafe for them to be alone. For example, people living with AD can wander and get lost, can be unable to manage their medications, and can forget important things like appointments.[25] This can have a negative effect on a person's independence and quality of life and can cause a lot of worry for their friends and family.

Additionally, there is no cure for AD and no treatment to slow or stop the progression of the disease.[26] AD can be a frightening diagnosis to receive, and support from friends, family and doctors is really important.[27]

Physical impact

AD also has an impact on physical health.[11] People with AD may have problems walking, be unsteady on their feet, find swallowing food more difficult or they may have seizures.[6] People with AD may also have problems with speaking and understanding people.[6] Changes to sleep patterns can also often occur in AD.[6] For example, waking frequently during the night.[6]

Later in the disease, as symptoms get worse, patients are less able to live independently and do everyday tasks.[11, 16] They will likely need help performing personal care tasks such as eating, washing and dressing.[24] Physical problems are often more noticeable at the later stage of the disease.[24] There is also an increase in the risk of falls.[24]

Impact on families and carers

Caring for someone with AD can be extremely challenging, due to changes in memory, behaviour and personality, including aggression in some cases.[11, 21] Aggression in the later stage of dementia is often a reaction to personal care. Someone may hit or push away those trying to help them.[24]

Caring full-time can leave family members feeling socially isolated and having to meet hidden costs.[21] Full-time caring can also impact on the caregiver's ability to continue engaging in aspects of their life such as work, resulting in loss of productivity.[28] It is predicted that 1.1 billion hours are spent each year on unpaid care for people with dementia.[29]

What is the personal and societal cost of Alzheimer's disease?

The costs of AD can be broken down into healthcare, social care and informal costs:

- Healthcare costs relate mainly to the NHS and are due to hospitalisation of people living with dementia.[22] Around 14% (£4.9 billion in 2019) of the total dementia costs in the UK are healthcare costs[19]
- Social care costs relate to services such as nursing homes, homecare, and respite care.[22] These make up 45% (£15.7 billion in 2019) of the total dementia costs in the

UK.[19] In England around 60.6% (around £8.3 billion in 2019) of the overall costs of social care are estimated to be met by the individual themselves and their families[15, 19]

- Informal or unpaid care costs relate to family providing unpaid care for people living with dementia.[22] These costs account for 40% (£13.9 billion in 2019) of total dementia care costs[19]

Societal cost

Most patients with AD dementia are cared for by a spouse or other family member.[28] Given how long AD can progress for, the strain on carers can be ongoing.[22]. Being dependent on a caregiver for everyday tasks can impact on both the person living with AD and the caregiver's ability to take part fully in activities such as work. This one of the biggest costs of AD to society.[28] However, this burden on families and society is often not fully captured in calculations of the costs of the disease.[28]

2b) Diagnosis of the condition (in relation to the medicine being evaluated)

Please briefly explain how the condition is currently diagnosed and how this impacts patients. Are there any additional diagnostic tests required with the new treatment?

How is Alzheimer's disease diagnosed?

Initial assessments[27, 30]

When someone has concerns about possible signs and symptoms of dementia, such as problems with memory, thought processes, concentration, communication and mood, they should see their doctor. The doctor will ask about the symptoms, how they are affecting the person's life and whether the person has a family history of dementia. To rule out other causes of memory loss, the doctors will investigate whether the person is experiencing depression, anxiety, stress, side effects from medication, substance abuse issues or other health problems (e.g., hormonal disturbances or nutritional deficiencies). They might also book a brain scan to check for other causes such as a stroke or brain tumour. However, even if a person is experiencing one of these conditions, an AD diagnosis can still be made.

The doctor will perform quick tests of the person's memory and cognitive abilities. Additionally, they may complete a physical examination and organise some blood tests. If dementia is suspected, they will make a referral to a **memory assessment service** or memory clinic. The doctor might diagnose MCI at this stage, without referral to the specialist memory service.

Memory assessment service

The memory clinic will perform more thorough tests of memory and cognition. These **cognitive tests** assess different abilities like memory, concentration, communication skills and awareness of time and place.[31] There are many cognitive tests available.

If the diagnosis or stage of the disease is still uncertain, the doctors may perform further tests such as brain scans. **Magnetic resonance imaging** (MRI) and **positron emission tomography** (PET) are the most common scans used in AD diagnosis.

Staging

There are three key stages of AD; mild AD (early stage), moderate AD (middle stage) and severe AD (late stage). Please see **Figure 1** in **Section 2a** for a summary of these stages.

2c) Current treatment options:

The purpose of this section is to set the scene on how the condition is currently managed:

- What is the treatment pathway for this condition and where in this pathway the medicine is likely to be used? Please use diagrams to accompany text where possible. Please give emphasis to the specific setting and condition being considered by NICE in this review. For example, by referencing current treatment guidelines. It may be relevant to show the treatments people may have before and after the treatment under consideration in this SIP.

Please also consider:

- if there are multiple treatment options, and data suggest that some are more commonly used than others in the setting and condition being considered in this SIP, please report these data.
- are there any drug–drug interactions and/or contraindications that commonly cause challenges for patient populations? If so, please explain what these are.

What are the current treatment options for Alzheimer's disease?

Currently, medicines available for AD only manage the symptoms. There is no evidence that these medicines change the course of the disease These medicines may provide small improvements in memory and thinking, and may help the person with daily tasks, but the disease itself continues to get worse.[23]

Acetylcholinesterase (AChE) Inhibitors

Three **AChE inhibitors** (donepezil, galantamine and rivastigmine) are recommended for mild to moderate AD.

Memantine

Memantine, a **N methyl-D-aspartate (NMDA) receptor antagonist,** is also recommended as an option for managing AD for people with:[32]

- moderate AD who are intolerant of or cannot take AChE inhibitors or
- severe AD

Non-Medicinal Treatment

Other than the medicines listed above, management of AD also includes social support, increasing assistance with day-to-day activities, information and education, carer support groups, community dementia teams, home nursing and personal care, community services such as meals-on-wheels, befriending services, day centres, respite care and care homes.[33]

2d) Patient-based evidence (PBE) about living with the condition

Context:

- **Patient-based evidence (PBE)** is when patients input into scientific research, specifically to provide experiences of their symptoms, needs, perceptions, quality of life issues or experiences of the medicine they are currently taking. PBE might also include carer burden and outputs from patient preference studies, when conducted in order to show what matters most to patients and carers and where their greatest needs are. Such research can inform the selection of patient-relevant endpoints in clinical trials.

In this section, please provide a summary of any PBE that has been collected or published to demonstrate what is understood about **patient needs and disease experiences**. Please include

the methods used for collecting this evidence. Any such evidence included in the SIP should be formally referenced wherever possible and references included.

Alzheimer's disease from the patient perspective

The What Matters Most (WMM) study interviewed patients with AD and their care partners. They were asked how their symptoms affect them. The study found that patients in early stages of AD experienced problems related to their symptoms, most commonly affecting their emotions, mood and social lives. The frequency of these problems increased with increasing stages of the disease. Care partners to patients in later stages of AD also experienced consequences related to the patient's symptoms. Particularly impacting the care partners' daily responsibilities and their emotions and mood. Taken together, these findings show that AD affects patients and their partners across the AD disease stages.[34]

A study by Dunn et al. (2022) supports these findings. This study used web-based profiles to ask patients and carers about AD symptoms. The biggest concerns in people with MCI and mild dementia were those that disrupted everyday life. These included problems caring for grandchildren or with participating in hobbies or games. Inappropriate behaviour, incontinence and eating were the next most important issues in people with MCI.[35]

Quality of life data collected within the clinical trial are presented in **Section 3f**. below.

SECTION 3: The treatment

3a) How does the new treatment work?

What are the important features of this treatment?

Please outline as clearly as possible important details that you consider relevant to patients relating to the mechanism of action and how the medicine interacts with the body

Where possible, please describe how you feel the medicine is innovative or novel, and how this might be important to patients and their communities.

If there are relevant documents which have been produced to support your regulatory submission such as a summary of product characteristics or patient information leaflet, please provide a link to these.

Donanemab is a **monoclonal antibody** used to treat AD in adults. Monoclonal antibodies are proteins that recognise and bind specifically to certain proteins in the body. Donanemab belongs to a group of medicines called **amyloid-targeting antibodies**. This medicine works by removing a sticky protein called beta-amyloid plaques from the brain which are known to contribute to the development of AD.

3b) Combinations with other medicines

Is the medicine intended to be used in combination with any other medicines?

- Symptomatic medicines, as discussed above, are likely to be allowed alongside donanemab treatment, as they were in the clinical trial

If yes, please explain why and how the medicines work together. Please outline the mechanism of action of those other medicines so it is clear to patients why they are used together.

If yes, please also provide information on the availability of the other medicine(s) as well as the main side effects.

If this submission is for a combination treatment, please ensure the sections on efficacy (3e), quality of life (3f) and safety/side effects (3g) focus on data that relate to the combination, rather than the individual treatments.

N/A

3c) Administration and dosing

How and where is the treatment given or taken? Please include the dose, how often the treatment should be given/taken, and how long the treatment should be given/taken for.

How will this administration method or dosing potentially affect patients and caregivers? How does this differ to existing treatments?

How is donanemab taken?

Donanemab is given by a healthcare professional, through a drip into the vein of the arm (**intravenous infusion**) over at least 30 minutes. After each infusion the person will be observed for allergic reactions for a minimum of 30 minutes.

How much medicine do patients take and when?

The recommended dose of donanemab is 1,400 mg. One dose of donanemab is usually given once every 4 weeks. When starting treatment with donanemab, the first three doses will be 700 mg once every 4 weeks.

3d) Current clinical trials

Please provide a list of completed or ongoing clinical trials for the treatment. Please provide a brief top-level summary for each trial, such as title/name, location, population, patient group size, comparators, key inclusion and exclusion criteria and completion dates etc. Please provide references to further information about the trials or publications from the trials.

Studies of donanemab in Alzheimer's disease

The main clinical trial that has studied donanemab for the management of adults with MCI due to AD or mild AD dementia is called **TRAILBLAZER-ALZ 2**. TRAILBLAZER-ALZ 2 was a **Phase 3** trial. This means they looked at how well donanemab worked to treat AD (its **efficacy**) and at the side effects linked to donanemab (its safety) compared to the standard treatment. The trial also looked at the impact of donanemab on patients' quality of life.

In TRAILBLAZER-ALZ 2, donanemab was compared to a **placebo**. This means a drug that seems real but has no medicinal benefit. Patients therefore received one of the following options:

1. Donanemab (700 mg for the first 3 doses and 1,400 mg thereafter)
2. Placebo

This study included patients with MCI or mild AD dementia with amyloid pathology shown with a valid test, which meant patients had to:

- Have memory problems for the last 6 months or more
- Have a cognitive test score within a certain range
- Have a brain scan which showed evidence of amyloid build-up
- Be aged between 60 and 85 years

A summary of the key information about the trial is provided in **Table 1**.

Table 1. Trials investigating donanemab

Trial name and number	Location	Number of patients included	Trial completion date
TRAILBLAZER-ALZ 2 (NCT04437511)	US, Australia, Canada, Czech Republic, UK, Japan, the Netherlands, and Poland	1800	14th April 2023[a]

[a]A long-term extension of the trial, to further assess the efficacy and safety of donanemab, is currently ongoing and is expected to complete 22nd August 2025.

More information about the TRAILBLAZER-ALZ 2 trial can be found here:

- **Document B**, **Section B.2.2**
- Sims JR et al. JAMA 2023;330(6):512–527. (https://jamanetwork.com/journals/jama/article-abstract/2807533)
- ClinicalTrials.gov (https://clinicaltrials.gov/study/NCT04437511)

3e) Efficacy

Efficacy is the measure of how well a treatment works in treating a specific condition.

In this section, please summarise all data that demonstrate how effective the treatment is compared with current treatments at treating the condition outlined in section 2a. Are any of the outcomes more important to patients than others and why? Are there any limitations to the data which may affect how to interpret the results? Please do not include academic or commercial in

confidence information but where necessary reference the section of the company submission where this can be found.

Trial results

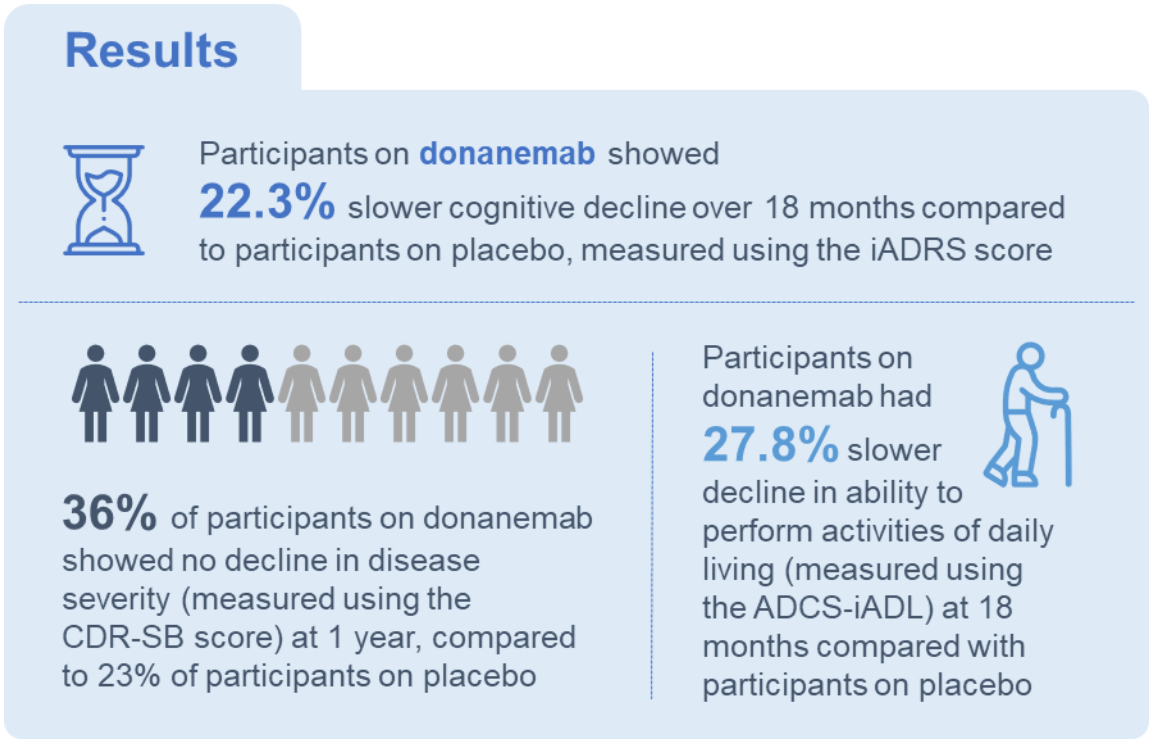
In the TRAILBLAZER-ALZ 2 trial, the efficacy of donanemab was measured according to how well it improved several key cognitive test measures after 76 weeks of treatment:

- **Integrated AD Rating Scale (iADRS) score**
- **Clinical Dementia Rating Sum of Boxes (CDR-SB) score**
- **AD Assessment Scale – Cognitive subscale (ADAS-Cog$_{13}$) score**
- **AD Cooperative Study – Activities of Daily Living Scale (ADCS-iADL) score**
- **Mini-Mental State Exam (MMSE) score**

These cognitive tests were used to show how much AD progressed over the time of the study, and whether donanemab slowed this progression or not.

Figure 2 shows the key efficacy results of the study after 76 weeks of treatment with donanemab. More efficacy results can be found in Document B, Section B.2.6.

Figure 2: Key efficacy results for TRAILBLAZER-ALZ 2 after 76 weeks of donanemab treatment



The efficacy of donanemab was also measured according to how well it reduced the build-up of amyloid and tau proteins in the brain after 76 weeks of treatment, measured with:

- A PET brain scan which measures amyloid
- A PET brain scan which measures tau

By 18 months, 76.4% of participants finished donanemab treatment because their amyloid plaques had cleared on these scans.

Additionally, participants on donanemab had a 37.4% lower risk of progressing to the next stage of disease compared to participants on placebo

3f) Quality of life impact of the medicine and patient preference information

What is the clinical evidence for a potential impact of this medicine on the quality of life of patients and their families/caregivers? What quality of life instrument was used? If the EuroQol-5D (EQ-5D) was used does it sufficiently capture quality of life for this condition? Are there other disease specific quality of life measures that should also be considered as supplementary information?

Please outline in plain language any quality of life related data such as **patient reported outcomes (PROs).**

Please include any **patient preference information (PPI)** relating to the drug profile, for instance research to understand willingness to accept the risk of side effects given the added benefit of treatment. Please include all references as required.

Quality of life impact of donanemab

During TRAILBLAZER-ALZ 2, patients were asked to answer questions about their **quality of life**, using a questionnaire called the Quality of Life – Alzheimer's disease (QoL-AD) scale.

The results from this questionnaire showed that there was no significant difference in quality of life at 76 weeks across the donanemab and placebo arms.[36, 37]

The trial design meant that differences in quality of life between groups could not be identified. The results indicate that treatment with donanemab did not negatively affect quality of life.

3g) Safety of the medicine and side effects

When NICE appraises a treatment, it will pay close attention to the balance of the benefits of the treatment in relation to its potential risks and any side effects. Therefore, please outline the main side effects (as opposed to a complete list) of this treatment and include details of a benefit/risk assessment where possible. This will support patient reviewers to consider the potential overall benefits and side effects that the medicine can offer.

Based on available data, please outline the most common side effects, how frequently they happen compared with standard treatment, how they could potentially be managed and how many people had treatment adjustments or stopped treatment. Where it will add value or context for patient readers, please include references to the Summary of Product Characteristics from regulatory agencies etc.

Every medicine has its own **side effects**, and the same medicine can produce different reactions in different people. To understand the side effects of donanemab, all medical

problems which happened during the TRILBLAZER-ALZ 2 trial were recorded. These are referred to as **adverse events**.

The most common adverse events experienced by patients receiving donanemab in TRILBLAZER-ALZ 2 were **amyloid-related imaging abnormalities** (ARIAs). These are differences seen on a brain scan. There are two types of ARIA: ARIA due to **oedema** or swelling (**ARIA-E**) or ARIA due to **microhaemorrhages** or bleeding (**ARIA-H**). The majority of ARIA cases were mild to moderate and were helped with appropriate management. ARIA is usually **asymptomatic**, although serious and life-threatening events can happen.

Adverse events which affected more or equal to 5% of patients in any group in TRAILBLAZER-ALZ 2 are summarised in Table 2 below:

Table 2. Summary of the most common adverse events experienced by patients during TRAILBLAZER-ALZ 2

Adverse events	Percentage of patients with this adverse event in TRAILBLAZER-ALZ 2	
	Donanemab	Placebo
ARIA-E	24.0	1.9
ARIA-H	19.7	7.4
COVID-19	15.9	17.6
Headache	14.0	9.8
Fall	13.4	12.6
Infusion-related reaction	8.7	0.5
Superficial siderosis of central nervous system	6.8	1.1
Dizziness	6.2	5.5
Arthralgia	5.7	4.8
Urinary tract infection	5.3	6.8
Diarrhoea	5.0	5.7
Fatigue	4.9	5.1

Note: further explanation of the terms in orange are provided in the glossary (Section 4b).

The proportion of patients who experienced a more serious adverse event or stopped their treatment (or “discontinued”) because of adverse events during TRILBLAZER-ALZ 2 is shown in Table 3. The most common adverse events that led to treatment discontinuation were infusion-related reactions, either ARIA-E or ARIA-H, and **hypersensitivity**.

The rate of serious adverse events was 17.4% in the donanemab group and 15.8% in the placebo group. In the donanemab group, 3 participants with serious ARIAs later died.

Some participants died during the course of the study; 1.9% in the donanemab group and 1.1% in the placebo group.

Table 3. Summary of serious adverse events and treatment discontinuations during TRAILBLAZER-ALZ 2

	Percentage of patients with this adverse event in TRAILBLAZER-ALZ 2

	Donanemab	Placebo
Participants with ≥1 serious adverse events (including death)	17.4	15.8
Adverse events leading to treatment discontinuation	13.1	4.3

Managing side effects

If symptoms of an allergic reaction happen during infusion, the infusion should be stopped immediately.

If a person gets any side effects, they should talk to their doctor, pharmacist or nurse. This includes any possible side effects not listed below. Reporting side effects can help provide more information on the safety of this medicine.

Side effects and how common they are:

- Very common (may affect more than 1 in 10 people) side effects include ARIAs and headaches. ARIAs are differences seen on a brain scan that are because of swelling. These can be with or without small spots of bleeding in or on the surface of the brain.
- Common (may affect up to 1 in 10 people) side effects are nausea, vomiting and infusion-related allergic reactions.
- Uncommon (may affect up to 1 in 100 people) side effects include sudden, severe allergic reaction with breathing difficulty, swelling, light-headedness, fast heartbeat, sweating, and loss of consciousness.

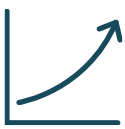
3h) Summary of key benefits of treatment for patients

Issues to consider in your response:

- Please outline what you feel are the key benefits of the treatment for patients, caregivers and their communities when compared with current treatments.
- Please include benefits related to the mode of action, effectiveness, safety and mode of administration

The key benefits of donanemab to patients with AD include that:

Donanemab is one of the first medicines that appears to change the course of the disease rather than just treat the symptoms



Donanemab slowed the progression of AD in the TRAILBLAZER-ALZ 2 trial on several tests of disease progression

Donanemab reduced amyloid plaque levels in the brain, as measured by PET brain scans. This could mean that some patients are able to complete treatment with donanemab sooner

Donanemab, if approved, may help people with early symptomatic AD to continue to participate in activities that are meaningful to them for longer

3i) Summary of key disadvantages of treatment for patients

Issues to consider in your response:

- Please outline what you feel are the key disadvantages of the treatment for patients, caregivers and their communities when compared with current treatments. Which disadvantages are most important to patients and carers?
- Please include disadvantages related to the mode of action, effectiveness, side effects and mode of administration
- What is the impact of any disadvantages highlighted compared with current treatments

Donanemab is effective in slowing cognitive decline in some patients, however, some things that patients may want to consider before starting treatment include:

Efficacy

Donanemab does not work for everyone and some patients might not experience any slowing of cognitive decline. Patients for whom donanemab does not work may still experience side effects, which are detailed further below.

Side effects

Like all medicines, some patients may experience side effects while they are taking donanemab. The most common side effects include ARIAs and headaches, nausea, vomiting and infusion-related allergic reactions. These are usually manageable, and most patients do not need to stop treatment because of these.

Administration

Donanemab must be taken through a drip in the vein of the arm (intravenous infusion) over at least 30 minutes once every 4 weeks. This means that donanemab must be taken at a hospital or clinic and cannot be taken at home. However, donanemab is taken every 4 weeks, and is stopped after 18 months or earlier when enough amyloid protein is cleared from the brain enough.

3i) Value and economic considerations

Introduction for patients:

Health services want to get the most value from their budget and therefore need to decide whether a new treatment provides good value compared with other treatments. To do this they consider the costs of treating patients and how patients' health will improve, from feeling better and/or living longer, compared with the treatments already in use. The drug manufacturer provides this information, often presented using a health economic model.

In completing your input to the NICE appraisal process for the medicine, you may wish to reflect on:

- The extent to which you agree/disagree with the value arguments presented below (e.g., whether you feel these are the relevant health outcomes, addressing the unmet needs and issues faced by patients; were any improvements that would be important to you missed out, not tested or not proven?)
- If you feel the benefits or side effects of the medicine, including how and when it is given or taken, would have positive or negative financial implications for patients or their families (e.g., travel costs, time-off work)?
- How the condition, taking the new treatment compared with current treatments affects your quality of life.

Healthcare administrators need to get the best value from their limited budgets. To do this, they want to know whether a new medicine provides 'good value for money' compared to existing medicines. They will look at the costs of the new medicine and how the health of patients is likely to improve if they take it. The pharmaceutical company that develops the medicines provides this information to healthcare administrators using a **health economic model**. The pharmaceutical company uses the health economic model to perform an analysis, which compares the costs and benefits of the new treatment (donanemab) with the standard of care (**best supportive care [BSC]**).

How the model reflects Alzheimer's disease

The health economic model estimates what would happen to people with AD with characteristics similar to those of people who would receive donanemab treatment in the NHS.

Modelling how much donanemab slows the rate of cognitive decline

The way treatment with donanemab affects AD was modelled using data from the TRAILBLAZER-ALZ 2 trial. Specifically, data from the CDR-SB scale were used, to provide information on how the disease progressed. Information from the 18-month trial was then used to estimate how effective donanemab would be over a longer period of time.

Modelling how much donanemab improves quality of life

The model measured changes to patient health as well as the impact of treatment on quality of life. This can include improvements in quality of life due to reduced symptoms. It can also include decreases in quality of life due to side effects of treatment.

Donanemab treatment helps to keep patients in the earlier stages of AD for longer. This improves quality of life. The model therefore included increased quality of life for patients in earlier stages of disease. The model also included reductions in quality of life whenever people experienced side effects of donanemab treatment. This included ARIA or infusion-related reactions. Estimates of quality of life were informed by published research or articles.

Modelling how the costs of treatment differ with donanemab

Various different costs are included in the model for donanemab. These costs include:

- The cost of purchasing the medicine itself
- The costs of administering the medicine (e.g., the healthcare professional time for administering the infusion)
- The costs of clinician time and other costs to the health service associated with treating AD
- The costs of diagnosing people with AD and the cost of monitoring for adverse events

Uncertainty

Several assumptions were made in the model that were validated by clinicians. Information on these assumptions can be found in **Document B, Section B.3.8.2**.

Variations of other inputs in the model were also tested and the results of these tests are explained in **Document B, Section B.3.10**.

Some aspects of the model are not completely certain and need further research. These include:

- Long-term evidence on the efficacy and safety of donanemab would provide more certainty. This is being tested in an extension to the TRAILBLAZER-ALZ 2 trial
- Costs of care for patients with AD by disease state are not completely certain, as there are limited data on these costs
- It is not certain how many people will be eligible for the treatment

Cost effectiveness results

The economic model showed that treatment with donanemab was associated with increased benefits and increased costs compared with BSC. The Committee will discuss how the assumptions made by the company to get their cost-effectiveness estimate match with what happens in practice in the NHS.

Full results of the cost-effectiveness analysis are presented in **Document B, Section B.3.9**.

3j) Innovation

NICE considers how innovative a new treatment is when making its recommendations.

If the company considers the new treatment to be innovative please explain how it represents a 'step change' in treatment and/ or effectiveness compared with current treatments. Are there any QALY benefits that have not been captured in the economic model that also need to be considered (see section 3f)

Donanemab is an innovative treatment which would represent an important advancement in the management of Alzheimer's disease

AD is a condition that can have a significant effect on a patient's mental and emotional wellbeing and quality of life. Despite this, there are no currently available treatment options that have been shown to be effective in slowing the disease.

Donanemab is an innovative medicine that treats the underlying cause of disease. It is the first of a group of treatments for AD that has strong evidence that shows it is effective in slowing disease progression in patients. Donanemab would therefore give patients the opportunity to experience disease slowing compared to current treatment options, reducing the negative impact that AD has on a patient's life.

3k) Equalities

Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged.

Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics

More information on how NICE deals with equalities issues can be found in the NICE equality scheme

Find more general information about the Equality Act and equalities issues here

There are no equality issues that are anticipated for the use of donanemab in adults with MCI or mild AD dementia.

SECTION 4: Further information, glossary and references

4a) Further information

Feedback suggests that patients would appreciate links to other information sources and tools that can help them easily locate relevant background information and facilitate their effective contribution to the NICE assessment process. Therefore, please provide links to any relevant online information that would be useful, for example, published clinical trial data, factual web content, educational materials etc.
Where possible, please provide open access materials or provide copies that patients can access.

Further information on Alzheimer's Disease:

- Alzheimer's Society website: https://www.alzheimers.org.uk/about-dementia/types-dementia/alzheimers-disease
- Alzheimer's Research UK website: https://www.alzheimersresearchuk.org/dementia-information/types-of-dementia/alzheimers-disease/
- Dementia UK website: https://www.dementiauk.org/information-and-support/types-of-dementia/alzheimers-disease/

Further information on NICE and the role of patients:

- Public Involvement at NICE Public involvement | NICE and the public | NICE Communities | About | NICE
- NICE's guides and templates for patient involvement in HTAs Guides to developing our guidance | Help us develop guidance | Support for voluntary and community sector (VCS) organisations | Public involvement | NICE and the public | NICE Communities | About | NICE

4b) Glossary of terms

This glossary explains terms highlighted in **black bold text** in this summary of information for patients. At times, an explanation for a term might mean you need to read other terms to understand the original terms.

Acetylcholinesterase (AChE) inhibitors	A medicine used to treat the symptoms of AD. They increase levels of acetylcholine, a substance in the brain that helps nerve cells communicate with each other.
Adverse event	An unexpected medical problem that arises during treatment, which may or may not be related to the treatment.
Amyloid	A protein that is found in the brain. In AD, it builds up and forms **plaques** that are thought to damage brain cells.
Amyloid beta pathology	When there is evidence of a build up of amyloid (specifically a type of **amyloid** protein called beta-amyloid) in the brain. This is usually shown with a brain scan, and helps to diagnose AD.

Amyloid-related imaging abnormality (ARIA)	ARIAs are differences seen on a brain scan that are thought to be related to drugs that target **amyloid**. There are two types of ARIA; **ARIA-E** and **ARIA-H**.
Amyloid-targeting antibody	Amyloid-targeting antibodies are a group of drugs that treat AD by targeting the **amyloid protein** in the brain.
ARIA-E	ARIA-E is a difference seen on a brain scan due to swelling or **oedema** in the brain.
ARIA-H	ARIA-H is a difference seen on a brain scan due to bleeding or **microhaemorrhages** in the brain.
Arthralgia	Joint stiffness or pain.
Asymptomatic	Producing or showing no symptoms.
Best supportive care (BSC)	Best supportive care is treatment that is focused on managing symptoms and helping to keep the individual as well as possible. This is given when there are no medicines that target or change the course of the disease, like in AD.
Clinical trial/clinical study	A type of research study that tests how well new medical approaches work in people. These studies test new methods of screening, prevention, diagnosis or management of a disease. Also called a clinical study.
Cognitive tests	Cognitive tests check how well a person's brain is functioning. They usually involve answering questions and performing simple tests.

Contraindication	A situation where a medicine should not be used because it might cause the person harm.
Dementia	A group of related symptoms associated with an ongoing decline of brain functioning.
Efficacy	The ability of a drug to produce the desired beneficial effect on your disease in a **clinical trial.**
Genes	Genes are the biological information in your cells that influence your traits, behaviours, and how your body functions; they are inherited from your parents and are essential in defining your individual characteristics.
Health economic model	A way to predict the costs and effects of a technology over time or in patient groups not covered in a **clinical trial**.
Hypersensitivity	Hypersensitivity is when your body has an exaggerated or abnormal response to a substance.
Incremental cost-effectiveness ratio	The incremental cost-effectiveness ratio (ICER), is the difference in the change in mean costs in the population of interest divided by the difference in the change in mean outcomes in the population of interest.
Intravenous infusion	Intravenous infusion, or IV, is a method of delivering fluids, medications, or nutrients directly into your veins through a small tube in your arm.
Magnetic resonance imaging (MRI)	This is a medical test that uses powerful magnets and radio waves to create detailed pictures of the inside of your body.

Marketing authorisation	The legal approval by a **regulatory body** that allows a medicine to be given to patients in a particular country.
Medicines and Healthcare products Regulatory Agency (MRHA)	The **regulatory body** that evaluates, approves and supervises medicines throughout the United Kingdom.
Memory assessment service	A specialist service for identifying **dementia**. People can be referred to these services by their GP.
Microhaemorrhages	Small bleeds on the brain.
Mild cognitive impairment (MCI)	A condition in which someone has minor problems with their mental abilities such as memory and thinking.
Monoclonal antibody	A type of **protein** that is made in the laboratory and can bind to certain targets in the body. Monoclonal antibodies are used in the management of many diseases, including AD.
N-methyl-D-aspartate (NMDA) receptor antagonist	NMDA receptor antagonists are medicines that work by blocking the effects of a chemical in the brain called glutamate. Memantine is an NMDA receptor agonist used for moderate or severe AD.
Net health benefit	A positive net health benefit means the model shows that more health will be generated by spending on this treatment than what NICE considers to be the average amount of health generated by NHS spending (£20,000 per quality adjusted life year)
Oedema	A build-up of fluid that causes swelling.
Plaques	A clump or build-up of something. In AD, **amyloid** builds up to form amyloid plaques.

Positron emission tomography (PET)	A procedure in which a small amount of radioactive substance is injected into a vein, and a scanner is used to make detailed, computerised pictures of areas inside the body.
Phase 3 clinical trial	This type of **clinical trial** that tests the safety and how well a new treatment works compared with a standard treatment. For example, it evaluates which group of patients has better survival rates or fewer **side effects**.
Placebo	A treatment that appears real but has no therapeutic benefit. It is used in clinical trials to compare treatments to.
Protein	These are structures inside all cells of our body that are important for many activities including growth and repair.
Quality-adjusted life year	A measure of the state of health of a person, where the length of life is adjusted to reflect the quality of life. One quality-adjusted life year (QALY) is equal to 1 year of life in perfect health. QALYs are calculated by estimating the years of life remaining for a patient following a particular treatment or intervention and weighting each year with a quality-of-life score (on a 0 to 1 scale). It is often measured in terms of the person's ability to carry out the activities of daily life, and freedom from pain and mental disturbance.
Quality of life	The overall enjoyment of life. Many **clinical trials** assess the effects of cancer and its treatment on the quality of life of patients. These studies measure aspects of a patient's sense of well-being and their ability to carry out activities of daily living.

Regulatory bodies	These are legal bodies that review the quality, safety and **efficacy** of medicines and medical technologies.
Side effect	An unexpected medical problem that is happens as a result of taking a treatment.
Superficial siderosis of central nervous system	A disease of the brain which can happen as a result of long-term bleeding in the brain.
Tangles	Abnormal build-up of **tau proteins**.
Tau	A protein found in the brain. This can build up in AD and form **tangles**.

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Donanemab for treating mild cognitive impairment or mild dementia caused by Alzheimer's disease [ID6222]

Clarification questions

February 2024

File name	Version	Contains confidential information	Date
ID6222_Donanemab Clarification Questions [CON]	1	Yes	14th March 2024

Notes for company

Highlighting in the template

Square brackets and grey highlighting are used in this template to indicate text that should be replaced with your own text or deleted. These are set up as form fields, so to replace the prompt text in [grey highlighting] with your own text, click anywhere within the highlighted text and type. Your text will overwrite the highlighted section.

To delete grey highlighted text, click anywhere within the text and press DELETE.

Section A: Clarification on effectiveness data

Decision problem

A1. The company submission (CS) (Table 1, pg 11) states that non-pharmacological management was included as a comparator in the decision problem addressed by the CS, for the MCI due to AD and mild dementia due to AD population.

a) **Please explain how non-pharmacological management has been incorporated into the modelling.**

Non-pharmacological management has not been considered in the economic model.

Based on clinical expert opinion, non-pharmacological management would be largely low cost with lifestyle advice and vascular risk management provided via information sheet and group cognitive stimulation delivered by allied health professionals. These costs are expected by clinical experts to be equal across treatment arms and Lilly therefore does not anticipate that inclusion of non-pharmacological management costs would have any meaningful impact on cost-effectiveness results.

Within the TRAILBLAZER-ALZ trial, non-medication treatments for AD such as behavioural management were permitted, but under the same restrictions as medication treatments taken for AD, such that they should remain constant when possible.

b) Please provide iADRS and CDR-SB outcomes separately for the subgroup of people who did not receive pharmacological management in addition to donanemab.

In the TRAILBLAZER-ALZ 2 trial, a subgroup analysis was conducted to assess iADRS and CDR-SB change from baseline in those who received acetylcholinesterase inhibitors (AChEIs) or memantine at baseline (i.e. pharmacological management) and those who did not, and no significant differences were found between the two subgroups for either outcome. Please refer to Table AACI.8.135 and Table AACI.8.145, in the TRAILBLAZER-ALZ 2 CSR.[1]

Specifically, in a natural cubic spline (NCS) model with 2 degrees of freedom, two interaction terms need to be considered to assess a potential interaction for a subgroup: one for the first part of the model (up to Month 9) and one for the second part of the model. Neither of the interactions for iADRS nor CDR-SB were significant: for iADRS, Baseline AChI/Memantine Use*treatment*spline1 p= 0.581 and Baseline AchI/Memantine Use *treatment*spline2 p=0.286; while for CDR-SB, Baseline AChI/Memantine Use*treatment*spline1 p= 0.317 and Baseline AChI/Memantine Use *treatment*spline2 p=0.368.

The results of the subgroup analyses in the overall population are presented in Table 1 for CDR-SB.

Table 1: Baseline AChEI/memantine use subgroup analysis for CDR-SB change from baseline by treatment (NCS2). Evaluable Efficacy Set

Subgroup	Time-Point	Treatment	Analysis Value			Differences (vs Comparator subgroup)			
			n	Mean (SD)	LS Mean (SE)	LS Mean Change(SE)	LS Mean Change Difference	95% CI	p-value
Baseline AChEI/memantine use (Yes)	Week 24	Placebo	483	5.09 (2.55)	5.13 (0.09)	0.83 (0.05)			
		Donanemab	445	4.72 (2.24)	4.76 (0.09)	0.47 (0.05)	-0.36 (0.07)	-0.499,-0.224)	<0.001
	Week 52	Placebo	424	5.80 (2.96)	6.09 (0.11)	1.80 (0.08)			
		Donanemab	396	5.28 (2.87)	5.47 (0.11)	1.18 (0.08)	-0.62 (0.11)	(-0.846, -0.398)	<0.001
	Week 76	Placebo	405	6.40 (3.27)	6.92 (0.13)	2.63 (0.11)			
		Donanemab	358	5.90 (3.26)	6.21 (0.14)	1.92 (0.11)	-0.71 (0.16)	(-1.017, -0.400)	<0.001
Baseline AChEI/memantine use (No)	Week 24	Placebo	301	3.81 (2.13)	4.02 (0.11)	0.57 (0.06)			
		Donanemab	286	3.66 (2.30)	3.77 (0.11)	0.33 (0.06)	-0.25 (0.09)	-0.421,-0.077)	0.005
	Week 52	Placebo	289	4.45 (2.64)	4.70 (0.14)	1.26 (0.10)			
		Donanemab	254	4.02 (2.68)	4.23 (0.14)	0.79 (0.10)	-0.48 (0.14)	(-0.755,-0.195)	<0.001
	Week 76	Placebo	267	4.89 (2.93)	5.30 (0.17)	1.86 (0.14)			
		Donanemab	240	4.28 (2.86)	4.69 (0.17)	1.25 (0.14)	-0.61 (0.20)	(-0.999, -0.230)	0.002

Abbreviations: AChEI: acetylcholinestersase inhibitor; CI: confidence interval; LS Mean: least-squares mean; n: number of patients at each visit with non-missing values; N: number of patients in the Evaluable Efficacy Set; SD: standard deviation; SE: standard error.
LS Mean Change from Baseline. SE, 95% CI and p-value are dervied by using natual cubic spline model with 2 degrees of freedom. The model was adjusted for basis of expansion terms (two terms), basis expansion term-by-treatment interaction, sub-group, basis expansion term-by-sub-group, 3 way interaction terms of basis expansion by term-by-sugroup-by-treatment, and covariastes for age at baseline, pooled investigator and tau category.

Background information and company SLR

A2. Please clarify why full-text original articles published before 2010 that were not included in the 2010 ERG SLR were excluded from the company's SLR for this appraisal (CS Appendix B.1.1.1, Table 1).

Full-text original articles published before 2010 that were not included in the 2010 ERG SLR, part of NICE appraisal TA217 of AChEIs and memantine,[2] were excluded from the SLR for this appraisal, because Lilly do not anticipate that any excluded studies would be relevant to the appropriate population for this decision problem, particularly as this is prior to the advent of clinical trials designed to assess disease-modifying therapies.

A3. Priority question: Categorising the severity of dementia due to Alzheimer's disease can vary between sources (and we note that in NICE TA217 paragraph 2.6 the MMSE severity score ranges slightly differ to those of the company: Mild Alzheimer's disease 21-26, moderate Alzheimer's disease 10-20). Please would the company indicate the score ranges defining MCI due to Alzheimer's disease and mild, moderate and severe dementia due to Alzheimer's disease for the scales used in the company's trial and provide the source reference for the severity ranges by completing the table below.

Severity ranges cannot be defined using scales other than MMSE or CDR, and so only CDR and MMSE are relevant to staging of the disease. Score ranges have therefore not been provided for ADAS-Cog_{13}, ADCS-iADL and iADRS. Score ranges for MMSE, CDR-G and CDR-SB are provided in Table 2.

Table 2: Score ranges defining MCI due to AD and mild, moderate and severe dementia due to AD, by scale

Scale	MCI due to AD	Mild dementia due to AD	Moderate dementia due to AD	Severe dementia due to AD	Source reference for severity ranges
ADAS-Cog_{13}	NR	NR	NR	NR	NR
ADCS-iADL	NR	NR	NR	NR	NR
CDR-SB	0, 4	4.5, 9	9.5, 15.5	≥16	O'Bryant *et al.* (2008)[3] and (2010)[4]
CDR-G	0.5	0.5 or 1	2	3	Morris *et al.* (1993)[5] and CDR Scoring Table[6]
iADRS	NR	NR	NR	NR	NR
MMSE[a]	≥27	20–26	10-19	<10	These ranges vary across sources and countries. To inform the economic

					modelling, we aligned with the cut-offs used in the TB2 clinical trial.[7]

[a]The minor differences in health state cut-offs between mild and moderate, as defined by MMSE, are not anticipated to have an impact on results.
Abbreviations: AD: Alzheimer's disease; ADAS-Cog$_{13}$: 13-Item Alzheimer's Disease Assessment Scale – Cognitive subscale; ADCS-iADL: Alzheimer's Disease Cooperative Study – Instrumental Activities of Daily Living Inventory; CDR-G: Clinical Dementia Rating Global score; CDR-SB: Clinical Dementia Rating–Sum of Boxes; iADRS: Integrated Alzheimer's Disease Rating Scale; MCI: Mild Cognitive Impairment; MMSE: Mini-Mental State Examination; NR: not relevant.

A4. CS Section B.1.3.4 describes the clinical pathway of care and reports information from an Adelphi survey (and the same survey is the source for information in CS Table 36?). Two excel spreadsheets containing results have been provided but with no context around these. Please provide full information for this survey (e.g. methods, population surveyed, date of survey etc.).

The Adelphi study protocol 'Eli Lilly Data on File. Adelphi DSP 2022-2023 Protocol' has been provided in the reference pack alongside these responses.[8] Published manuscripts that provide further detail on the methodology of the study have also been included within the reference pack (Anderson *et al*. 2008; Babineaux *et al.* 2016; Higgins *et al.* 2016).[9-11]

TRAILBLAZER-ALZ 2 and TRAILBLAZER-ALZ trials

A5. Priority question: Please provide the trial protocols for TRAILBLAZER-ALZ and TRAILBLAZER-ALZ 2.

The published trial protocols 'TRAILBLAZER-ALZ Protocol I5T-MC-AACG(d)' and 'TRAILBLAZER-ALZ2 Protocol I5T-MC-AACI(e)' have been provided in the reference pack alongside these responses.[12, 13]

A6. CS section B.2.3.2 states that elevated tau was used as an enrichment criterion in the phase 3 trial. Please explain how this enrichment was achieved (e.g. did the eligibility criteria allow for a greater proportion of patients with elevated tau to be enrolled than was present in the screened population?).

In both the TRAILBLAZER-ALZ (Phase 2) and TRAILBLAZER-ALZ 2 (Phase 3) studies, initiation of donanemab treatment required evidence of the presence of amyloid and tau pathology, which was provided by amyloid and tau PET scans. The low-medium (or intermediate) tau group was defined to be a relatively homogenous group on a continuum of tau pathology. No stratification between low and medium tau was defined or employed. Any method to stratify between low and medium tau may not correspond to a clinically meaningful segmentation.

The designation of low-medium tau PET signal was based on a systematic exploration of results from previous observational and therapeutic clinical trials. The ^{18}F-AV-1451 PET Imaging Study (NCT02016560) was a cross-sectional and longitudinal observational study evaluating imaging characteristics of flortaucipir in healthy participants and patients with MCI and AD dementia.[14] It

was conducted in two phases: a phase 2 exploratory phase and a phase 3 confirmatory phase. In the exploratory and confirmatory cohorts of the flortaucipir PET trial, both quantitative estimates of tau PET signal (a global AD signature-weighted neocortical SUVR; Pontecorvo *et al.* 2019)[15] and visual interpretation (Lu et al. 2021)[16] were associated with a rate of cognitive decline over an 18-month period. Thus, eligibility criteria for tau PET in TRAILBLAZER-ALZ and TRAILBLAZER-ALZ 2 were based on both a visual read and quantitation.

Quantitative baseline tau PET was stratified by the inter-quartile ranges established in the exploratory and confirmatory cohorts of the flortaucipir PET trial. The specific thresholds were as detailed in Table 3 below.

Table 3: Baseline tau PET thresholds and associated inter-quartile ranges.

Quartile	Tau SUVR
First	<1.1
Second – Third (inter-quartile range)	1.1–1.46
Fourth	>1.46

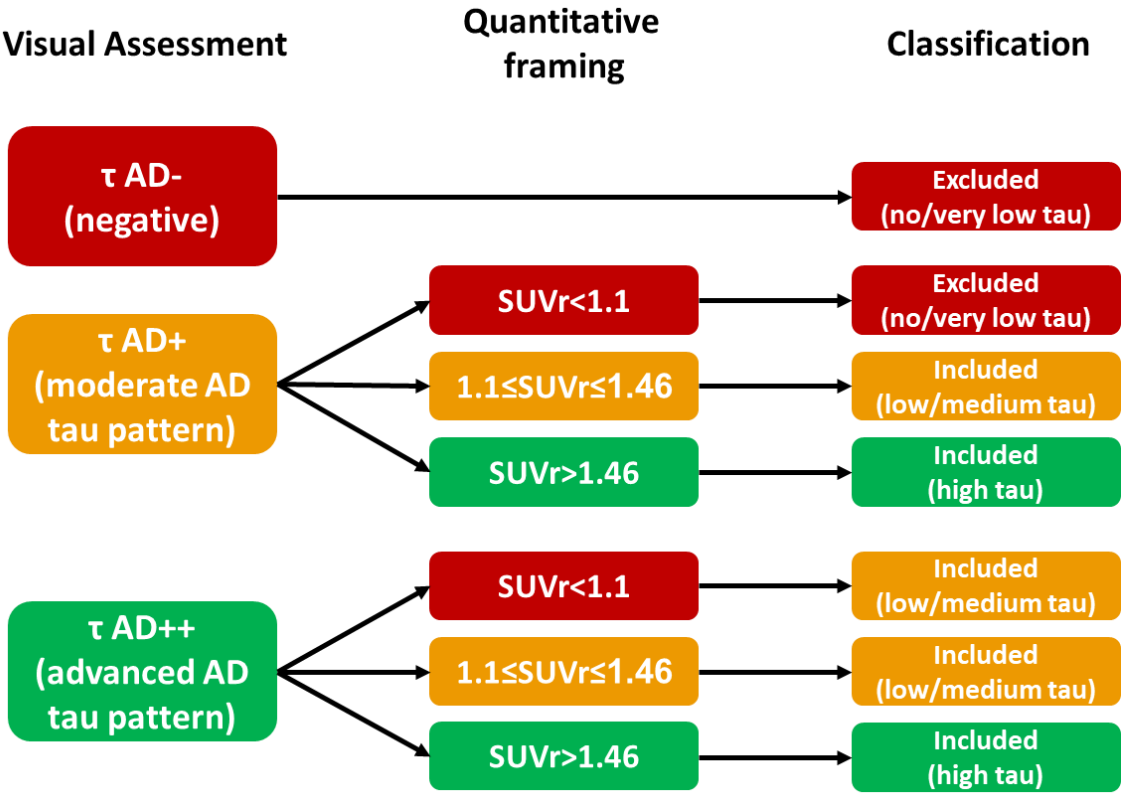
Abbreviations: PET: positron emission tomography; SUVR: standardized uptake value ratio.

The first quartile and those without evidence of advanced tau on visual read were not included in TRAILBLAZER-ALZ 2 because participants were considered to have a slower 18-month clinical progression, and efficacy demonstration would require trials of length greater than 18 months. The first quartile was classified as no/very low tau. The no/very low tau group included participants with a negative flortaucipir PET visual read (τ AD-), or a moderate visual read (flortaucipir PET signal limited to posterior lateral temporal cortex, τ AD+) and a global AD signature volume of interest SUVR less than 1.10 (Figure 1).

Participants were enrolled into TRAILBLAZER-ALZ 2 based on an advanced tau visual read (with flortaucipir PET signal beyond the temporal cortex, τ AD++) or a moderate visual read (τ AD+) and a global AD signature-weighted SUVR greater than or equal to 1.10. Of the enrolled participants, those with a global AD signature-weighted SUVR greater than 1.46 were stratified to the high tau cohort in TRAILBLAZER-ALZ 2, whereas the remaining enrolled participants were stratified to the low-medium (intermediate) tau cohort (Figure 1). The exclusion of no to very low tau individuals would slightly enrich for a higher tau population than in the general early symptomatic AD population.

It should be noted that participants with a global AD signature-weighted SUVR greater than 1.46 were excluded from the TRAILBLAZER-ALZ trial, whereas they were stratified into the high tau group in the TRAILBLAZER-ALZ 2 trial. This exclusion was based on the observation that the longitudinal rate of increase in tau PET signal approaches asymptote in some brain regions (Pontecorvo et al. 2019)[15] leading to the hypothesis that participants with high tau (for example, SUVR greater than 1.46) may be experiencing more downstream neurodegenerative effects and a more rapid rate of deterioration. Thus, while the benefit of an amyloid-targeting therapy in this population was expected to be observed (as was demonstrated in TRAILBLAZER-ALZ 2), the observed percentage slowing of cognitive decline may have been smaller for this population and could have limited the opportunity to demonstrate clinical efficacy in the smaller phase 2 TRAILBLAZER-ALZ study.

Figure 1: Tau enrichment criteria for the TRAILBLAZER-ALZ 2 trial



Abbreviations: AD: Alzheimer's disease; τ AD-: negative tau visual read; τ AD+: moderate tau visual read; τ AD++: advanced tau visual read; SUVr; standardised uptake value ratio.

When information regarding tau pathology is available, it adds additional insight on the stage and course of disease, and particularly can augment traditional symptom evaluation as an enrichment tool for clinical trials. However, considering that favourable donanemab treatment effects were evident across baseline tau groups and given its targeted mechanism of action, treatment with donanemab is indicated in patients with evidence of Aβ pathology.

A7. CS Table 6 states that use of symptomatic and nonmedication treatments for AD were permitted in the TRAILBLAZER-ALZ2 trial. Please provide details about the specific symptomatic and nonmedication treatments used by participants in each trial arm, and comment on how reflective these are of those used in practice. Please indicate what proportion of patients with mild cognitive impairment due to Alzheimer's disease in each trial arm received symptomatic treatment with acetylcholinesterase inhibitors or memantine.

Non-medication treatments were not routinely captured in the trial. However, a full list of concomitant medications used during the trial can be found in Table AACI.8.7 of the TRAILBLAZER-ALZ 2 CSR provided in the reference pack.[1] The most frequently used concomitant medications are detailed in Table AACI.4.7 in the study CSR,[1] and in Table 4 below.

Table 4: Most frequently used concomitant medications in the TRAILBLAZER-ALZ 2 trial

Concomitant Medication, n (%)	Placebo (N = 874)	Donanemab (N = 853)	Total (N = 1727)
Donepezil	[redacted]	[redacted]	[redacted]
COVID-19 vaccine	[redacted]	[redacted]	[redacted]
Acetylsalicylic acid	[redacted]	[redacted]	[redacted]
Colecalciferol	[redacted]	[redacted]	[redacted]
Atorvastatin	[redacted]	[redacted]	[redacted]
Memantine	[redacted]	[redacted]	[redacted]
Paracetamol	[redacted]	[redacted]	[redacted]

Abbreviations: COVID-19: coronavirus disease 2019; N: number of participants in the population; n: number of participants in the specified category.

Baseline characteristics for patients with MCI due to AD (based on MMSE score at screening) are provided in the Reference Pack alongside these responses ('Eli Lilly Data on File. Baseline Characteristics MCI MMSE Screening'), with AChEI and memantine use data on page 8.[17] Please see a summary of medication use in patients with MCI due to AD (MMSE score 27–30 at screening) by treatment arm in Table 5.

These data are in line with data from a recent Adelphi survey which reported that [redacted] MCI patients used off-label AChEI.

Table 5: Medication use in patients with MCI due to AD at screening, based on MMSE

Medication use, n(%)	Placebo (N = 137)	Donanemab (N = 146)	Total (N = 283)
AChEI and/or memantine use at screening	78 (56.9)	58 (39.7)	136 (48.1)
AChEI use at screening	74 (54.0)	54 (37.0)	128 (45.2)
Memantine use at screening	21 (15.3)	17 (11.6)	38 (13.4)

Abbreviations: AChEI: acetylcholinesterase inhibitor; AD: Alzheimer's disease; MCI: mild cognitive impairment.

The use of concomitant symptomatic AD treatment remained stable during the course of TRAILBLAZER-ALZ 2 and neither the introduction of new concomitant AD use, nor dose changes to existing AD symptomatic medication affected the result of donanemab being superior to placebo for either of the iADRS or CDR-SB outcomes.

106 (12.1%) participants in the placebo group and 69 (8.1%) participants in the donanemab group started a new concomitant AD symptomatic medication (such as acetylcholinesterase inhibitors or memantine). 50 (5.7%) participants in the placebo group and 27 (3.2%) participants in the donanemab group changed the dose of an existing AD medication (see Table APP.141 in 'Eli Lilly Data on File. Concomitant Medications (Table APP.141–143)' provided in the Reference Pack).[18]

Both "New or any change of concomitant medication" and "No change of concomitant medication" subgroups showed donanemab to be superior to placebo on both iADRS (Table APP.142)[18] and CDR-SB (Table APP.143).[18] Given that placebo-treated participants were more likely to start new concomitant AD medications, the extent of the separation between participants treated with donanemab and placebo may have been diminished due to temporary iADRS and

CDR-SB performance improvements in the placebo-treated group.

A8. Priority question: MMSE at screening and baseline

a) CS Table 7 provides information on the TRAILBLAZER-ALZ 2 population screening MMSE category and the baseline MMSE category. CS Figure 5 suggests that the time between screening and baseline was 7 weeks. Please would the company confirm if our understanding that the time difference of 7 weeks is correct or if this varied by participant. If the period varied by participant what was the average time difference (with range or SD).

The time between screening and baseline in the TRAILBLAZER-ALZ 2 trial was on average 11.1 weeks. Please see Table 6 below for summary statistics from MMSE measurement time intervals.

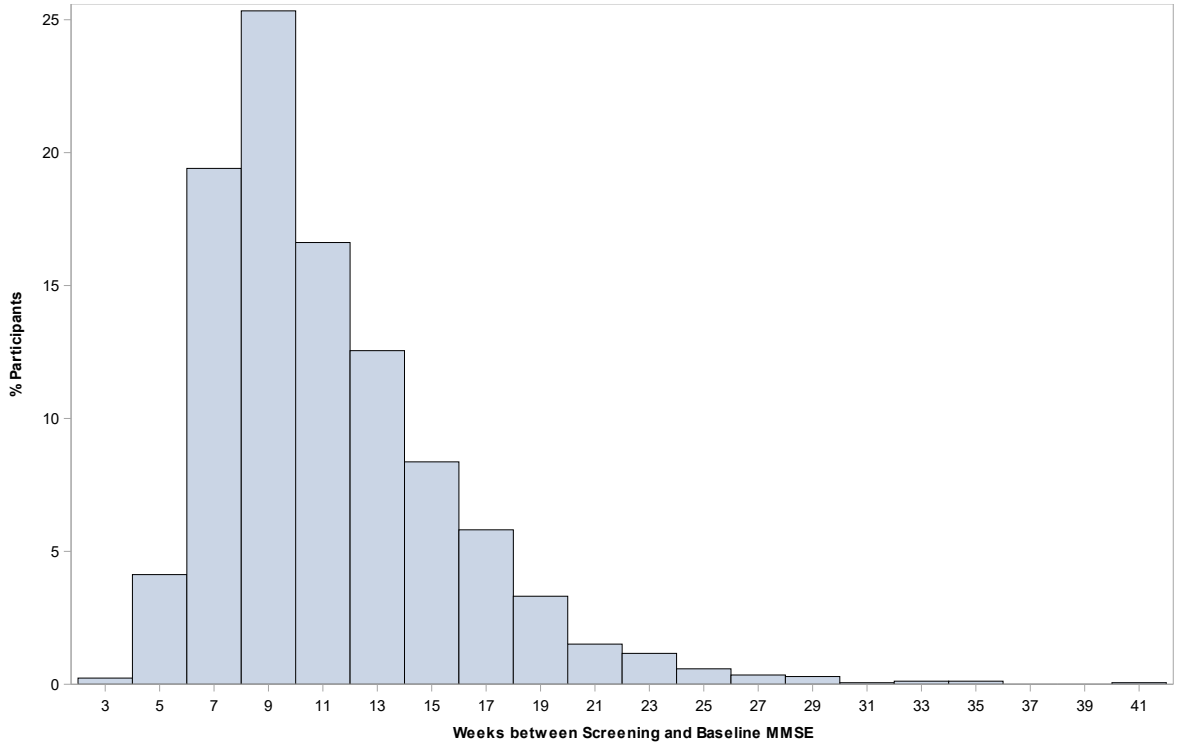
Table 6: Summary of MMSE measurement time intervals between screening and baseline.

Time interval (weeks)	Placebo (N = 871)	Donanemab (N = 850)	Total (N = 1,721)
Mean (SD)	11.0 (4.26)	11.1 (4.65)	11.1 (4.45)
Median	10.0	10.0	10.0
Min, Max	2.4, 28.9	3.7, 41.9	2.4, 41.9

Abbreviations: Min: minimum; Max: maximum; SD: standard deviation.

As per the protocol,[12] if a screen failure was due to an MMSE score >28, then one rescreen was allowed after 24 weeks. The histogram below (Figure 2) shows the distribution of the percentage of patients by time interval in weeks, highlighting that approximately 45% of patients were screened and randomised between 6 and 10 weeks. There are some outliers with longer time intervals, which is due to patients being allowed to be rescreened after 24 weeks, as outlined above and in the protocol.

Figure 2: Summary of MMSE measurement time intervals between screening and baseline in the TRAILBLAZER-ALZ 2 trial



Abbreviations: MMSE: Mini Mental State Examination.

Clinical experts consulted by Lilly thought that the time gap between identifying an eligible patient in clinical practice and initiating treatment would be shorter in clinical practice than in the trial. They estimated that this gap would be 4–8 weeks in length and highlighted that this would not be long enough for meaningful progression that would stop patients from being eligible for treatment.

b) What is the explanation for the difference between screening and baseline proportions of participants falling within each of the MMSE categories? Is this solely due to disease progression between the two timepoints? Also, why is the total number of patients included in the baseline MMSE categories [redacted] less than the total number of patients at screening?

Assessment of disease stage is broader than performance on MMSE, due to within-patient variation in MMSE. MMSE performance has also been shown to be moderated by education and age, with less educated and older individuals tending to receive lower scores.[19] In addition, confounding factors such as dehydration, particularly when surpassing 2% body mass loss,[20] and sleep quality have been shown to impair cognitive function.[21] . It is possible that such factors may translate into variations in cognitive performance and in part account for the increase in patients classified as moderate at baseline. It is therefore unlikely that the difference between screening and baseline is solely due to disease progression between the two timepoints.

Additionally, clinical experts consulted by Lilly highlighted that it is unlikely that this number of patients will progress to moderate AD within 4–8 weeks, the anticipated time period between screening and baseline in clinical practice.

Finally, Lilly can confirm that the total number of patients included in the baseline MMSE categories are [redacted] less than the total number at screening because [redacted] patients have missing MMSE at baseline, and [redacted] patients have a baseline MMSE lower than 10 ([redacted] patient scored 6 and [redacted] patients scored 8).

c) Please can the company confirm that all the other data in Table 7 comes from baseline measurements (not screening)?

Lilly can confirm that this is correct, except for the biomarker measures (amyloid plaque level and AD signature weighted neocortical flortaucipir SUVR) as these were only performed at screening. All other specific AD measurements in Table 7 were conducted at baseline.

A9. Priority question: Eligible population: CS Table 2 states the anticipated population eligible for donanemab treatment will be "[redacted]

a) CS Table 7 shows that [redacted]% of the donanemab arm and [redacted]% of the placebo arm of the TRAILBLAZER-ALZ 2 RCT had moderate AD based on their baseline MMSE category. Please would the company comment on whether these patients would be eligible to initiate treatment with donanemab using the anticipated wording for the proposed licenced indication.

Patients deemed to be in the moderate AD disease stage at screening will not be eligible to initiate treatment on donanemab, based on the anticipated licence indication statement. As noted in the response to Question A8b, assessment of disease stage is, however, broader than MMSE score alone and is considered alongside other clinical assessments. As noted in response to Question 8a above, the anticipated timeline between screening and treatment initiation in NHS practice would be relatively short and would not allow sufficient time for significant disease progression.

b) CS Figures 11 and 12 show subgroup analyses for the iADRS and the CDR-SB respectively with three groups for clinical stage [MCI (≥27); Mild AD (20-26), Moderate AD (<20)]. We presume these clinical stages are categorised by MMSE score at baseline. Is there a subgroup analysis for the MCI and Mild AD groups at baseline combined as this would appear to be the relevant group of patients for this appraisal.

The clinical stages referred to in Figures 11 and 12, were indeed categorised by MMSE score at

baseline; with moderate AD defined by an MMSE score of <20, mild AD defined by MMSE score of 20–26 and MCI defined by an MMSE score of ≥27.

The hazard ratio of disease progression for donanemab vs BSC for the combined MCI and mild AD population based on the MMSE baseline score is provided in Question B2b.

As expected, given the non-significant interactions discussed in Section B.3.2.2 of the CS and the subgroup analyses performed in the TRAILBLAZER-ALZ 2 clinical study report (Figures 11 and 12 in the CS), the hazard ratio in this subpopulation does not differ much from the hazard ratio estimated in the overall population. The HR and associated 95%CI in the requested subpopulation are [redacted] and 0.623 [0.519, 0.748] for the overall population.

It is worth noting that, according to KOL feedback, MMSE score can vary by up to 3 points from day-to-day, depending on how the patient is currently feeling. As such, Lilly do not think it is appropriate to exclude the patients with moderate AD at baseline according to MMSE score.

A10. Priority question: Please provide screening and baseline characteristics for MCI, mild AD and moderate AD categories as determined by the CDR-SB (i.e. similar to the data provided in CS Table 7 for screening and baseline MMSE categories but using the CDR-SB to determine MCI, mild AD and moderate AD instead).

Demographics and baseline characteristics tables for MCI, mild Ad and moderate AD categories as determined by the CDR-SB are provided in Table 7 below. Please note that these assessments were conducted at baseline, and only MMSE scores were measured at screening.

Table 7: Screening and baseline CDR-SB characteristics in the overall population

Characteristics	Overall population	
	Donanemab (n=860)	Placebo (n=876)
Screening CDR-SB category, n (%)[a]		
MCI (0, 4)	Not collected	Not collected
Mild AD (4.5, 9)	Not collected	Not collected
Moderate AD (9.5, 15.5)	Not collected	Not collected
Baseline CDR-SB category, n (%)		
MCI (0, 4)	507 (59.0)	532 (60.7)
Mild AD (4.5, 9)	323 (37.6)	321 (36.6)
Moderate AD (9.5, 15.5)	15 (1.7)	16 (1.8)

Footnotes: [a] Based on screening data.
Abbreviations: AD: Alzheimer's Disease; CDR-SB: Clinical Dementia Rating–Sum of Boxes; MCI: mild cognitive impairment.
Source: Eli Lilly Data on File: Baseline Characteristics CDR-SB MCI;[22] Baseline Characteristics CDR-SB Mild;[23] Baseline Characteristics CDR-SB Moderate.[24]

A11. Footnote g to CS Table 7 states "Baseline MMSE category figures do not match with the moderate numbers in the forest plots as the baseline characteristics

values represent the ITT population rather than the analysed population". Which forest plots are being referred to in this footnote?

The forest plots being referred to in this footnote are Figure 11 and 12 in the CS, which present the baseline characteristic subgroup analyses in the overall population for the iADRS and the CDR-SB, respectively.

A12. CS Appendix B.2, Figure 3, shows the number and proportion of participants who discontinued the study in each of the TRAILBLAZER-ALZ 2 trial arms, along with the reasons for discontinuation. [redacted] participants in the placebo arm and [redacted] in the donanemab arm appear to be unaccounted for in the flow of participants between treatment allocation and "Completed PC" in each arm (i.e. they are not accounted for in the numbers discontinuing the study). Are these the [redacted] participants mentioned in the footnote who did not complete the final visit prior to the database lock? If not, please clarify what happened to these participants.

The 12 participants mentioned in the footnote of CS Appendix B.2, Figure 3 refer to the participants who did not complete the final visit prior to database lock (five participants in the placebo arm and seven participants in the donanemab arm). This is also detailed in Sims *et al.* 2023 Figure 1.[7]

Statistical analysis of the TRAILBLAZER-ALZ 2 trial

A13. Priority question: The company defines six analysis populations in CS Table 8 and describes the statistical methods for the primary analysis in CS Table 9 but without clearly stating which of the analysis populations the primary analysis is conducted for. CS Section B.2.6.1 reports results for the primary endpoint (iADRS), the key secondary endpoint (CDR-SB) and other secondary endpoints stating that these are in the 'overall population' which is not one of the populations defined in CS Table 8 . Please would the company confirm if the 'overall population' in CS B.2.6.1 aligns with the 'evaluable efficacy' population (also described as the modified intent-to-treat population) defined in CS Table 8.

In the TRAILBLAZER-ALZ 2 trial, participant randomisation was stratified by tau pathology. The low-medium tau population and overall population (i.e. all tau patients, the combined low-medium and high tau populations) were primary analysis populations in the study.

N numbers in Table 8 of the CS are referring to the statistical analysis sets for all participants (i.e. the overall population). The primary analysis was conducted in the Evaluable Efficacy population (both in the low-medium and overall populations).

A14. Priority question: Please provide the statistical analysis plans for TRAILBLAZER-ALZ and TRAILBLAZER-ALZ 2 trials.

The published statistical analysis plan for TRAILBLAZER-ALZ and TRAILBLAZER-ALZ 2 have been provided in the reference pack as 'TRAILBLAZER-ALZ SAP v3' and 'TRAILBLAZER-ALZ 2 SAP v3' alongside these responses.[25, 26] An addendum to the statistical analysis plan for TRAILBLAZER-ALZ 2, 'Eli Lilly Data on File. TRAILBLAZER-ALZ 2 Supplemental SAP',[27] has also been provided in the reference pack, which includes the QoL-AD measure described in B.2.6.4 of the CS.

A15. Priority question: Was the primary analysis performed with or without imputation of missing values?

No imputation was performed for the primary analysis in the evaluable efficacy set.

A16. Priority question: Were any analyses conducted for the full ITT population as a sensitivity analysis (e.g. by imputing missing values?). If such analyses were conducted, please describe these and provide the results.

The Evaluable Efficacy Set, the population that the primary efficacy analyses were based upon, is a modified ITT population (including participants with a baseline and at least one postbaseline efficacy measurement based on randomised treatment). Multiple sensitivity analyses were conducted using the ITT population using various assumptions on missing data within the efficacy analyses. The details of these ITT-based analyses are described below.

The missing values at baseline were first imputed using the average from the placebo arm, which allows for the multiple imputation for other visits, especially for the participants who did not have any measurements throughout the trial. Then two sets of analyses were conducted, one set with a 'missing at random' assumption, and one set included missing imputation with a 'missing not at random' assumption.

Missing imputation with missing at random assumption

For this analysis, the missing values were imputed based on a missing at random assumption, and when calculating for missing values, the imputation model included flags for participants who discontinued treatment during the trial, or participants who experienced an amyloid related imaging abnormality (ARIA) event. The missing imputation was run 30 times, and the final model estimations from each completed dataset were combined following Rubin's rule.

Missing imputation with a missing not at random assumption (imputation with the lowest 20% responders and a with jump to reference method)

For participants who discontinued from the study due to death or an ARIA AE, the missing values were multiple imputed based on the lowest 20% change scores seen across treatment arms. For all other intercurrent events leading to permanently missing data in the treatment arm, as well as for the participants without postbaseline assessment, a jump to reference multiple imputation was conducted to impute for the missing values. The missing values were imputed for 30 rounds, which generated 30 completed datasets. Corresponding models were run with each completed dataset, and lastly the modelled estimations (e.g., LS mean changes) from each dataset were combined following Rubin's rule to give the final score changes by treatment, difference between

treatment, and the associated 95% confidence intervals and p-values.

Results of the sensitivity analyses

Table 8 summarises CDR-SB and iADRS results at Week 76 for the two imputation methods. These results demonstrate the robustness of the pre-specified analyses and support the conclusion that treatment with donanemab slowed the progression of disease relative to placebo.

Table 8: Analysis results for iADRS and CDR-SB at Week 76 using the two different imputation methods

Analysis	Population	Donanemab versus Placebo p-value		Source
		LS mean change Difference (SE; 95% CI)	p-value	
Missing imputation with missing at random assumption				
CDR-SB MMRM analyses at Week 76[1]	Overall	[redacted]	[redacted]	Eli Lilly Data on File. CDR-SB MAR[28]
iADRS NCS2 analyses at Week 76[2]	Overall	[redacted]	[redacted]	Eli Lilly Data on File. iADRS MAR[29]
Missing imputation with a missing not at random assumption				
CDR-SB MMRM analyses at Week 76[3]	Overall	[redacted]	[redacted]	Eli Lilly Data on File. CDR-SB Not MAR[30]
iADRS NCS2 analyses at Week 76[4]	Overall	[redacted]	[redacted]	Eli Lilly Data on File. iADRS Not MAR[31]

Abbreviations: CI: confidence interval; LS Mean: least-squares mean; MMRM: Mixed Method Repeated Measure; SE: standard error; NCS2: natural cubic spline with 2 degrees of freedom.

[1]LS mean change from baseline, SE, 95% CI and p-value are derived using mixed model repeated measures methodology with fixed factors for treatment, visit, treatment-by-visit interaction, and covariates for baseline score, baseline score-by-visit interaction, baseline tau category, pooled investigators, concomitant AchEI or memantine use at baseline, and age at baseline. *Imputation method:* multiple imputation with indicators of discontinued treatment and ARIA occurrence as covariates

[2]LS mean change from baseline, SE, 95% CI and p-value are derived using natural cubic spline model with 2 degree of freedom. The model was adjusted for basis expansion terms (two terms), basis expansion term-by-treatment interaction, and covariates for age at baseline, pooled investigator, baseline tau category, and baseline AChI/Memantine use. *Imputation method:* multiple imputation with indicators of discontinued treatment and ARIA occurrence as covariates

[3]LS mean change from baseline, SE, 95% CI and p-value are derived using mixed model repeated measures methodology with fixed factors for treatment, visit, treatment-by-visit interaction, and covariates for baseline score, baseline score-by-visit interaction, baseline tau category, pooled investigators, concomitant AchEI or memantine use at baseline, and age at baseline. *Imputation method:* If patient discontinued due to death or ARIA, multiple imputation using observed values from the lower 20% of change scores seen in the whole trial; otherwise, impute with a jump to reference.

[4]LS mean change from baseline, SE, 95% CI and p-value are derived using natural cubic spline model with 2 degree of freedom. The model was adjusted for basis expansion terms (two terms), basis expansion term-by-treatment interaction, and covariates for age at baseline, pooled investigator, baseline tau category, and baseline AChI/Memantine use. *Imputation method:* If patient discontinued due to death or ARIA, multiple imputation using observed values from the lower 20% of change scores seen in the whole trial; otherwise, impute with a jump to reference.

Adverse events

A17. Priority question: ARIA-H and Superficial siderosis

a) CS Table 14 shows treatment emergent adverse events with ARIA-H and superficial siderosis of central nervous system shown as separate entries whereas in CS Table 15 superficial siderosis is shown as a sub-component of ARIA-H. Please could the company clarify if the superficial siderosis of central nervous system events shown in CS Table 14 are also included with the ARIA-H events in CS Table 14 or if they are in addition to the ARIA-H events.

Because ARIA-H findings (e.g. microhaemorrhage) are often asymptomatic (otherwise referred to as silent), it was up to the investigator discretions as to whether to report these MRI observations as adverse events. However, in CS Table 15 all findings based on MRI and/or TEAE cluster are reported, as noted in the footnote [a]. This ensures that CS Table 15 captures any MRI findings that were either reported (in CS Table 14) or not reported as adverse events, as well as the very rare instances in which no central read MRI was available, though local read identified new ARIA-H findings that were reported as adverse events.

b) Please could the company explain why in CS Table 14 the superficial siderosis of central nervous system events number 58 in the donanemab arm and 10 in the placebo arm of TRAILBLAZER-ALZ 2 but CS Table 15 shows 134 and 26 events of superficial siderosis in the donanemab and placebo arms respectively within the ARIA-H events.

As detailed in the response to part (a), CS Table 14 in Document B includes adverse events reported in the AE case report form whereas CS Table 15 includes both ARIAs reported in the AE case report form as wells as ARIAs that were identified via MRI and reported on a specific ARIA case report form. Observations should not be double counted between CS Tables 14 and 15 since CS Table 15 includes all possible observations, so AEs captured in CS Table 14 will also be captured in CS Table 15.

A18. Priority question: Meta-analysis

a) Please explain your rationale for not conducting meta-analysis of the TRAILBLAZER-ALZ and TRAILBLAZER-ALZ 2 trials for the iADRS (primary endpoint of both trials) and CDR-SB (key secondary endpoint of TRAILBLAZER 2, secondary outcome of TRAILBLAZER-ALZ) given both trials support the application for marketing

authorisation and the CDR-SB hazard ratio is used to model treatment effect in the economic model.

The rationale for not conducting a meta-analysis of the TRAILBLAZER-ALZ and TRAILBLAZER-ALZ 2 trials is that there is heterogeneity between the studies which limits the feasibility and validity of a meta-analysis. A key difference between the studies is that the populations of the trials are not aligned. The TRAILBLAZER-ALZ trial only includes patients with low-medium tau, so a meta-analysis cannot be carried out in the population that is relevant to this decision problem, the overall population. Additionally, there are study design differences between the trials, such as treat-to-clear strategy and exclusion criteria that make the outcome of a meta-analysis of the trials inappropriate. Please see Table 9 below for a comparison of the study design of the two trials.

Table 9: Study design comparison of the TRAILBLAZER-ALZ and TRAILBLAZER-ALZ 2 trials

Study design	TRAILBLAZER-ALZ (phase 2)[32]	TRAILBLAZER-ALZ 2 (phase 3)[7]
Tau exclusion criteria	Patients with a high tau level (a PET SUVR of >1.46) were excluded from the trial.	Tau PET scans were categorised as low-medium or high tau, but none were excluded on this basis.
Randomisation stratification	By investigative site only.	By investigative site and baseline tau categorisation.
Treat-to-clear strategy	If amyloid plaque level was 11 to <25 centiloids on any one PET scan, the dose was lowered to 700 mg. If the amyloid plaque level was less than 11 centiloids on any one scan or was 11 to less than 25 centiloids on two consecutive scans, donanemab was switched to placebo.	If amyloid plaque level was <11 Centiloids on any single PET scan or <25 but ≥11 Centiloids on 2 consecutive PET scans, donanemab was switched to placebo.

Abbreviations: PET: positron emission tomography; SUVR: standardized uptake value ratio.

b) Please conduct meta-analyses of the TRAILBLAZER-ALZ and TRAILBLAZER-ALZ 2 trials for the iADRS and CDR-SB outcomes.

Please see the response to part (a) for a detailed discussion on why meta-analyses of the TRAILBLAZER-ALZ and TRAILBLAZER-ALZ 2 trials have not been conducted.

c) Please add an option to use the result from the meta-analysis in the economic model.

Please see the response to part (a) for a detailed discussion on why meta-analyses of the TRAILBLAZER-ALZ and TRAILBLAZER-ALZ 2 trials have not been conducted, and therefore why an option to use the meta-analysis result in the economic model has not been added.

Section B: Clarification on cost-effectiveness data

In response to some of the queries made by the EAG within the following questions, the base case economic model has been updated. The following updates have been made:

- Calculation of disutility value associated with anaphylactic reaction

The updated probabilistic base case results are presented in Table 10. To note, all other scenario analyses have been presented deterministically.

Table 10: Probabilistic updated base-case results

Technologies; mean (95% CI)	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER versus baseline (£/QALY)
Severity modifier applied						
Donanemab	[redacted]	7.77	2.18			
BSC	[redacted]	7.75	1.34	£13,867.35	0.84	£16,579.18
No severity modifier applied						
Donanemab	[redacted]	7.78	1.83			
BSC	[redacted]	7.75	1.13	£13,715.24	0.71	£19.395.33

Abbreviations: BSC: best supportive care; ICER: incremental cost-effectiveness ratio; LYG: life years gained; QALY: quality-adjusted life year.

Published cost-effectiveness studies

B1. Please provide the full list of the included and excluded published cost-effectiveness studies with the corresponding reasons for exclusion.

Please see the Economic SLR study list Excel 'Eli Lilly DoF Donanemab in AD eSLR Study List' provided in the Reference Pack alongside these responses.[33] Studies that were initially excluded based on their title/abstract (n=1,065) can inspected by filtering the table by Column L, and studies that were excluded during full screening (n=57) can be inspected by filtering the table by Column M. The reasons for exclusion can then be found in column N. Both levels of exclusion (title/abstract and full screening) followed the PICOS eligibility criteria outlined in Table 11 of Appendix E.1.1.1. of the CS.

Population/baseline characteristics

B2. According to CS page 55, "a substantial number of patients were considered to be in the moderate AD category at baseline."

a) Please clarify how these patients were accounted for in the economic model. In which health state do these patients start the model?

The patients in the model start in MCI and mild AD, in line with the anticipated indication wording for donanemab. The percentages of patients were adjusted and the overall N was the sum of the

patients considered MCI due to AD and mild AD dementia at baseline. However, all patients were considered in the treatment effect analysis.

b) Please explain the impact of including a substantial number of patients with moderate AD dementia in the treatment effect outcomes.

Within the design of TRAILBLAZER-ALZ 2, it is intentional that at **screening** patients fit the criteria of MMSE 20–28 commensurate with MCI due to AD and mild AD dementia. The study design serves to assess treatment effect based on amyloid clearance. Donanemab is a limited duration treatment option whereby full treatment effect is not met until the patient has cleared amyloid or they stop after a maximum of 18 months treatment. The design intentionally continues to treat patients until amyloid cleared or maximum of 18 months, independent of whether patients transition from MCI to mild or mild to moderate/severe stage of disease. It is imperative that the course of treatment is given to ensure patients treatment is not stopped prematurely and allows the maximum effect of the treatment on cognitive and functional decline associated with amyloid clearance.

A subgroup analysis for combined MCI due to AD and mild AD dementia at baseline groups was conducted although Lilly do not anticipate treatment effect to differ across severity groups based on subgroup analyses (Figures 11 and 12 in the CS) and interaction effects discussed in Section B.3.2.2 of the CS. Specifically, disease severity is not considered a treatment effect modifier based on an interaction test completed (using the Cox proportional hazard [CPH] model described in Section B.2.6.5 of the CS) investigating the interaction of AD severity by the study treatment variable. The results of this were not statistically significant with the p-value of the interaction of the AD severity category (screened according to the MMSE score) on the CDR-SB being 0.6286.

The hazard ratio for disease progression based on the CDR-SB scale and derived from the TRAILBLAZER-ALZ 2 trial was used to model treatment effect for donanemab relative to BSC.[7] The HR with moderate AD patients at baseline according to a single MMSE score removed is presented in Table 11 below and the results of the scenario analysis utilising this HR are presented in Table 12. The interpretation of the cost-effectiveness results is unchanged, whether using HR modelled in original company submission or the HR shown in Table 11.

Table 11: Hazard ratio of disease progression for donanemab versus BSC (CDR-SB scale)

HR vs. BSC	MCI due to AD, mild AD dementia at baseline (moderate AD dementia removed)
Donanemab	[redacted]

Abbreviations: AD: Alzheimer's Disease; BSC: best supportive care; CDR-SB: Clinical Dementia Rating Scale – Sum of Boxes; HR: hazard ratio; MCI: mild cognitive impairment.

Table 12: Scenario analyses (donanemab PAS price) – HR excluding patients with moderate AD dementia at baseline

Technologies	Inc. costs (£)	Inc. QALYs	ICER (£/QALY)
Original base case (severity modifier)	£13,953.18	0.85	£16,466.70
Original base case (no severity modifier)	£13,953.18	0.71	£19,736.03
HR excluding patients with moderate AD	£13,059.76	0.89	£14,684.70

dementia (severity modifier)			
HR excluding patients with moderate AD dementia (no severity modifier)	£13,059.76	0.74	£17,621.64

Abbreviations: ICER: incremental cost-effectiveness ratio; Inc. incremental; PAS: patient access scheme; QALY: quality-adjusted life year.

B3. Please clarify how the number of caregivers per patient used in the model base case were derived (CS Table 48)

Within the model it was assumed that there were 1.8 caregivers per patient. This assumption was based on data from the GERAS EU study, an 18-month prospective, multicentre, naturalistic, observational cohort study reflecting the routine care of patients with AD in France, Germany, and the UK.[34, 35] The mean number of caregivers participating in caring for the patient in the pooled cohort (n=1,497) as well as in the individual UK cohort (N=526) was 1.8 (SD: 1.1).[35.]

Model structure

B4. Please clarify whether the company model structure was based on any published source.

As described in Appendix E of the CS, an SLR of economic evaluations was conducted as part of the model development process. The results of the SLR were used to understand the benefits and drawbacks of previously used model structures and to inform model selection. However, the model was developed *de novo* and is not based on any specific published source.

As discussed in Section B.3.1.3 of the CS, NICE HTA Lab report noted that economic models in AD should be "*transparent and can be easily interrogated and validated within the evaluation timelines will increase the credibility of its outputs and be more informative for decision making."* Further, the International PharmacoEconomic Collaboration on Alzheimer's Disease (IPECAD) modelling workshop challenge noted that due to the complexity of AD, it is important '*to balance simplicity and complexity in modelling it to capture the relevant key features of the disease without heavily relying on unvalidated data, statistical associations or assumptions'.*

Treatment effectiveness

B5. Priority question: Treatment effectiveness in the model

a) **The Clinical Dementia Rating Sum of Boxes (CDR-SB) change from baseline is described as a key secondary endpoint for the TRAILBLAZER-ALZ 2 trial and the TRAILBLAZER-ALZ trial (whereas the primary outcome in both trials was the iADRS change from baseline). CS section B.2.3.1 states there are many neuropsychological tests available for measuring disease severity**

and progression of MCI due to AD and mild AD dementia but no single test is recognised as the gold standard. Please would the company explain their rationale for choosing the CDR-SB as the measure of disease progression in the health economic model (i.e., what do the company perceive as the advantages of the CDR-SB over the other neuropsychological tests, particularly the primary outcome iADRS, conducted for the TRAILBLAZER-ALZ and -ALZ 2 trials?)

The iADRS provides an integrated assessment of cognition and daily function. As a continuous measure, the iADRS total score provides a fit-for-purpose primary endpoint for assessment of changes in cognition and daily function within clinical trials for early symptomatic AD. In contrast, CDR was developed and validated as a clinical staging instrument supporting ordinal classification of individual patients into one of 5 distinct disease stages (no impairment, questionable/MCI, mild AD, moderate AD, severe AD).

As a clinical staging instrument, the CDR serves as the established, widely accepted measure of evaluating and modelling progression between these clinically defined disease stages across the full spectrum of the disease. In addition, these disease stages can directly be linked to level of independence, and therefore costs and resource utilisation, which is of particular importance in cost-effectiveness modelling. Applying the treatment effect of the CDR to the disease staging based on the CDR increases consistency across the model and reduces uncertainty caused by the use of different scales. In addition, unlike the CDR-SB, the other scales included as outcome assessment tools in the trial (i.e. ADAS-COG-13, MMSE, ADCS-iADL) assess either cognitive or functional domains but not both. On this basis, Lilly maintains that CDR-SB is the most appropriate scale to use to model the treatment effect as was provided in the original company submission base case.

b) Please explain what amount of change in CDR-SB is required to move from one health state to another.

The health state boundaries as defined by CDR-SB score are provided in Table 17 of Question B16. The amount of change that is required to move from one health state to another is dependent on the initial health state.

Unfortunately, there is an error in the clinical worsening definition given in Section B.2.6.5 of the CS, where the hazard ratio (HR) of progressing to clinical worsening between donanemab and BSC is described. The definition should be as follows:

- A 1-point or more increase in CDR-SB from baseline for participants with baseline clinical status of MCI due to AD, or a 2-point increase from baseline for participants with baseline clinical status of mild AD dementia.

The remaining overview of the HR analysis described in Section B.2.6.5. of the CS is correct.

c) Please add the option of applying a hazard ratio of progressing to clinical worse health states between donanemab and BSC from the iADRS measure to the economic model.

The option of applying a hazard ratio of progressing to clinical worse health states between donanemab and BSC from the iADRS measure has now been added to the economic model. Cost-effectiveness results using this option are presented in Table 13 below.

The hazard ratio analysis based on the iADRS measure has been modelled in the same way as with the CDR-SB measure, but with a clinical worsening defined as:

- A ≥5-point decrease in iADRS for MCI due to AD and a ≥9-point decrease in iADRS for mild AD dementia participants.

This hazard ratio analysis was also modelled as time to first occurrence of the event and included the same covariates as the CDR-SB option. Additionally, as with the CDR-SB option, a clinical worsening event was defined as meeting the clinical worsening criteria at two consecutive visits during the double blinded phase, as described in Section B.2.6.5 of the CS. The proportional hazard assumptions also hold for this model.

The hazard ratio when using this model was 0.700 (0.582, 0.842) as presented in the Sims *et al.* (2023) supplementary material.[7]

Table 13: Scenario analyses (donanemab PAS price) – HR of progression using iADRS scale

	Inc. costs (£)	Inc. QALYs	ICER (£/QALY)
Original base case (severity modifier)	£13,953.18	0.85	£16,466.70
Original base case (no severity modifier)	£13,953.18	0.71	£19,736.03
HR of progression using iADRS scale (severity modifier)	£18,372.65	0.65	£28,395.27
HR of progression using iADRS scale (no severity modifier)	£18,372.65	0.54	£34,074.32

Abbreviations: ICER: incremental cost-effectiveness ratio; Inc. incremental; PAS:; patient access scheme; QALY: quality-adjusted life year.

d) Please provide an overview of the baseline, 12, 24, 36, 52, 64 and 76 weeks (both % and N) based on the trial, using i) the MMSE and ii) CDR-SB to define health states.

Please see below for a summary of the number of patients occupying each health state in both treatment arms across the trial, as defined by MMSE score (Table 14), and by CDR-SB score (Table 15).

Table 14: Number of patients throughout the TRAILBLAZER-ALZ 2 trial who occupy each health state defined by MMSE score

Treatment	MMSE scores n/N (%)	Baseline	Week 12	Week 24	Week 36	Week 52	Week 64	Week 76
Placebo		853	837	799	758	724	678	685
	MMSE scores [27-30]	122 (14.3)	136 (16.2)	111 (13.9)	108 (14.2)	93 (12.8)	91 (13.4)	75 (10.9)
	MMSE scores [20-26]	512 (60.0)	452 (54.0)	442 (55.3)	378 (49.9)	355 (49.0)	294 (43.4)	299 (43.6)
	MMSE scores [19 -10]	216 (25.3)	246 (29.4)	242 (30.3)	268 (35.4)	260 (35.9)	275 (40.6)	283 (41.3)
	MMSE scores <10	3 (0.4)	3 (0.4)	4 (0.5)	4 (0.5)	16 (2.2)	18 (2.7)	28 (4.1)
Donanemab		822	786	744	699	660	602	608
	MMSE scores [27-30]	141 (17.2)	145 (18.4)	151 (20.3)	120 (17.2)	100 (15.2)	96 (15.9)	97 (16.0)
	MMSE scores [20-26]	497 (60.5)	427 (54.3)	384 (51.6)	375 (53.6)	329 (49.8)	289 (48.0)	270 (44.4)
	MMSE scores [19 -10]	184 (22.4)	212 (27.0)	206 (27.7)	200 (28.6)	225 (34.1)	208 (34.6)	220 (36.2)
	MMSE scores <10	0 (0.0)	2 (0.3)	3 (0.4)	4 (0.6)	6 (0.9)	9 (1.5)	21 (3.5)

Abbreviations: MMSE: Mini Mental State Examination.

Table 15: Number of patients throughout the TRAILBLAZER-ALZ 2 trial who occupy each health state defined by CDR-SB score

Treatment	CDR-SB scores n/N (%)	Baseline	Week 12	Week 24	Week 36	Week 52	Week 64	Week 76
Placebo		851	829	787	754	715	680	676
	CDR-SB Scores [0-4]	523 (61.5)	454 (54.8)	390 (49.6)	364 (48.3)	294 (41.1)	266 (39.1)	248 (36.7)
	CDR-SB Scores [4.5-9]	312 (36.7)	343 (41.4)	361 (45.9)	337 (44.7)	341 (47.7)	327 (48.1)	337 (49.9)
	CDR-SB Scores [9.5-15.5]	16 (1.9)	31 (3.7)	34 (4.3)	50 (6.6)	77 (10.8)	84 (12.4)	86 (12.7)
	CDR-SB Scores ≥16	0 (0.0)	1 (0.1)	2 (0.3)	3 (0.4)	3 (0.4)	3 (0.4)	5 (0.7)
Donanemab		819	783	738	689	658	608	606
	CDR-SB Scores [0-4]	495 (60.4)	449 (57.3)	413 (56.0)	361 (52.4)	326 (49.5)	295 (48.5)	274 (45.2)
	CDR-SB Scores [4.5-9]	309 (37.7)	314 (40.1)	301 (40.8)	300 (43.5)	281 (42.7)	251 (41.3)	268 (44.2)
	CDR-SB Scores [9.5-15.5]	15 (1.8)	19 (2.4)	24 (3.3)	28 (4.1)	51 (7.8)	60 (9.9)	58 (9.6)
	CDR-SB Scores ≥16	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.3)	6 (1.0)

Abbreviations: CDR-SB: Clinical Dementia Rating Scale – Sum of Boxes.

e) Please discuss whether a mapping function between CDR-SB and MMSE is available.

Lilly is not aware of a mapping function between CDR-SB and MMSE which captures the full range of the disease, in particular in the earlier stages. A study assessing how scores on the ADAS-Cog, MMSE, and CDR-SB correspond in 1,709 participants showed good correspondence across the scores. However, MMSE scores in the study do not go below 20, so the mapping between the scores is not available for the full range of the disease. The study notes the superiority of CDR-SB in precisely measuring the severity of cognitive dysfunction over MMSE.[36] A further study correlated MMSE scores with CDR in 863 patients, and substantial agreement was obtained between the MMSE range and the CDR for the categories of mild, moderate, and severe dementia.[37] The agreement between the two instruments was moderate for no dementia and fair for questionable dementia, concluding that the MMSE can be used as a surrogate measure for the CDR in the staging of dementia due to AD.

It is also important to note that the MMSE does not assess functioning, which is critical to staging of disease severity, while the CDR was developed and validated as a clinical staging instrument supporting ordinal classification of individual patients into one of 5 distinct disease stages (see also question B5a).

f) Please elaborate on the implications (including the potential impact on the cost-effectiveness results) of using CDR-SB defined health states (instead of MMSE).

The health states in the model were not strictly defined by any one measure of disease severity, but the health state transition probabilities in the model were informed by the CDR-SB score. As demonstrated by the data provided in the response to part (d) and (e) above, CDR-SB provides a more precise measure for staging the severity of disease. Overall, the implications of using CDR-SB rather than MMSE are that model state transitions are based on a more robust disease measurement scale which is consistent with the scale used to assess treatment effect, reducing uncertainty in the model, while state definitions are broader but well aligned with the scale used for the transitions.

g) Please justify informing the CS model, using CDR-SB defined health states, with health state utility values and costs data categorised based on the MMSE.

Health states are not strictly defined based on any one measure of disease severity. It is very challenging to fully align all data inputs with a certain measure of disease severity, due to the heterogeneity in how disease severity is defined; it must be considered that the approach in clinical practice is rightly more holistic than relying on any single measure of cognitive or functional impairment, not least as each measure may exhibit day-to-day variability.

h) Please elaborate on the transferability of health state utility values and costs data categorised based on the MMSE to CDR-SB defined health states.

As mentioned in the response above, health states are not strictly defined based on any one measure of disease severity, and it is challenging to fully align all data inputs with a certain measure of disease severity. In fact, the meta-analysis used for informing the patient quality of life inputs in the model are based on a number of studies using different scales to define disease stages, including but not limited to MMSE and CDR-SB.

Finally, as confirmed by KOL feedback, in routine clinical practice it is expected that the approach to clinically diagnose patients with MCI due to AD or AD dementia is more holistic than relying on a single measure of cognitive or functional impairment.

i) Please provide scenario analyses, as well as an updated version of the economic model, using MMSE to define health states.

In line with the reasons outlined in the previous responses to this question, scenario analyses using MMSE to define health states would not be appropriate and have therefore not been conducted. The rationale for not conducting these scenarios is that firstly, as detailed in part (a) of this question, the CDR-SB is a well-validated outcome measure used for more than 20 years in clinical trials of AD and MCI.[38] It is an established tool for assessing treatment effect in other models of early AD, and defining health states using CDR-SB score ensures consistency in the model, which uses CDR-SB for key inputs. Further, the data in part (d) demonstrate that CDR-SB-defined health states are more consistent across the trial compared with MMSE-defined health states, which show more variability. In addition, the MMSE is a scale which was developed to assess cognitive impairment, while the CDR assesses impact on cognition and function. It is important to assess functional decline as AD impacts functionality. Tombaugh and McIntyre highlighted in their review on the MMSE that the scale discriminates well in the later stages of the disease but is less sensitive in the early stages of the disease.[39] Finally, as discussed in part (g), assessment of health states is broader than performance on any one measure, due to the heterogeneity in how disease severity is defined, as often the approach is more holistic than relying on a single measure of cognitive or functional impairment.

B6. In CS Table 48, it is stated that “the treatment effect sourced from the trial accounts for the chance of inclusion of any false positive diagnoses in the trial”. Please clarify whether the risk of false positive diagnoses with a PET scan is expected to be similar or not to the risk of false positive diagnoses with a lumbar puncture.

During an Office of Market Access (OMA) meeting held in July 2023, clinical experts noted that they would not expect differences in concordance between PET scans or CSF testing for confirmation of amyloid positivity.

Additionally, the results of a PET/CSF concordance study conducted by Lilly found that CSF was non-inferior compared to amyloid PET scans in identifying amyloid positive patients. The study also found that CSF testing was able to identify the same amyloid-positive patients as amyloid PET scans (Table 16). It is therefore expected that the risk of false positive diagnoses with a PET scan to be similar to the risk of false positive diagnoses with a CSF test.[40]

Table 16: Agreement of CSF and amyloid PET

Reference standard	Amyloid-PET quantitation (n=288)	Amyloid-PET quantitation (n=251)
CSF assay (label threshold)	Lumipulse CSF Aβ42/40 % (95% CI)	Elecsys CSF P-tau181/Aβ42 % (95% CI)
Positive percent agreement	98.29 (95.08–99.42)	91.38 (86.26–94.71)
Negative percent agreement	82.30 (74.24–88.24)	85.71 (76.20–91.83)
Overall percent agreement	92.01 (88.30–94.62)	89.64 (85.26–92.83)
Positive predictive value	89.58 (84.46–93.16)	93.53 (88.79–96.35)
Negative predictive value	96.88 (91.21–98.93)	81.48 (71.67–88.4)

Abbreviations: Aβ: beta-amyloid; CI: confidence interval; CSF: cerebrospinal fluid; PET: positron emission tomography.

B7. Priority question: The hazard ratio of progressing to clinical worse health states between donanemab and BSC was estimated using a Cox proportional hazard model (CS section B.2.6.5 page 54). Please provide evidence that the proportional hazard assumption holds.

The proportional hazard assumption for the Cox proportional model used to estimate the hazard ratio (HR) of progressing to clinical worse health states (as described in Section B.2.6.5) was visually assessed with:

- the Kaplan–Meier curves,
- the log cumulative hazard plot,
- the standardised Schoenfeld residuals of Grambsch and Therneau (1994)
    - The standardised Schoenfeld residuals were generated with the R package after fitting the Cox-proportional hazard model with the same covariates used to estimate the donanemab treatment effect (i.e., adjusting for baseline age, score, and concomitant AChEI and/or memantine use at baseline (yes/no), and stratifying by pooled investigator sites, and baseline tau category)

Figure 3 displays the Kaplan–Meier curves for each treatment arms of the TRAILBLAZER-ALZ 2 data and Figure 4 displays the log cumulative hazards. The steps seen in both the Kaplan–Meier and log cumulative hazard curves correspond to the scheduled visits as per protocol. Figure 5 displays the smoothed standardized Schoenfeld residuals over time, with associated 95% confidence interval, and the p-value of the test performed on these residuals (with the null hypothesis that the slope of these residuals over time equals to zero). A “no effect” horizontal line was added in red colour.

Based on visual assessment of the Kaplan–Meier curves (curves are not crossing) and on the log cumulative hazard plot (parallel hazards), there is evidence that the proportional hazards assumption holds. In addition, the inspection of the smoothed standardised Schoenfeld residuals over time, adds evidence that the hazards are proportional as they constitute an approximate horizontal line. Finally, the p-value from the test performed on those residuals is p=0.506 suggesting that the assumption of slope=0 for those residuals cannot be rejected. In other words, there is no evidence of violation of the proportional hazard assumption; the treatment effect is constant over time.

Figure 3: Kaplan–Meier curves for TRAILBLAZER-ALZ 2 trial

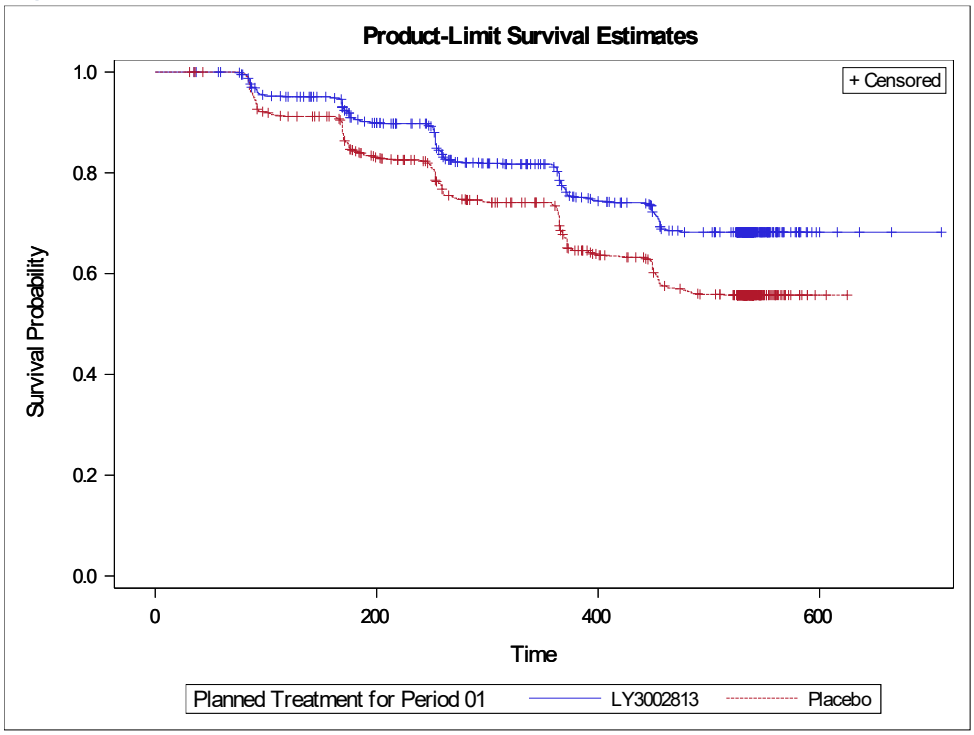


Figure 4: Log cumulative hazard plot

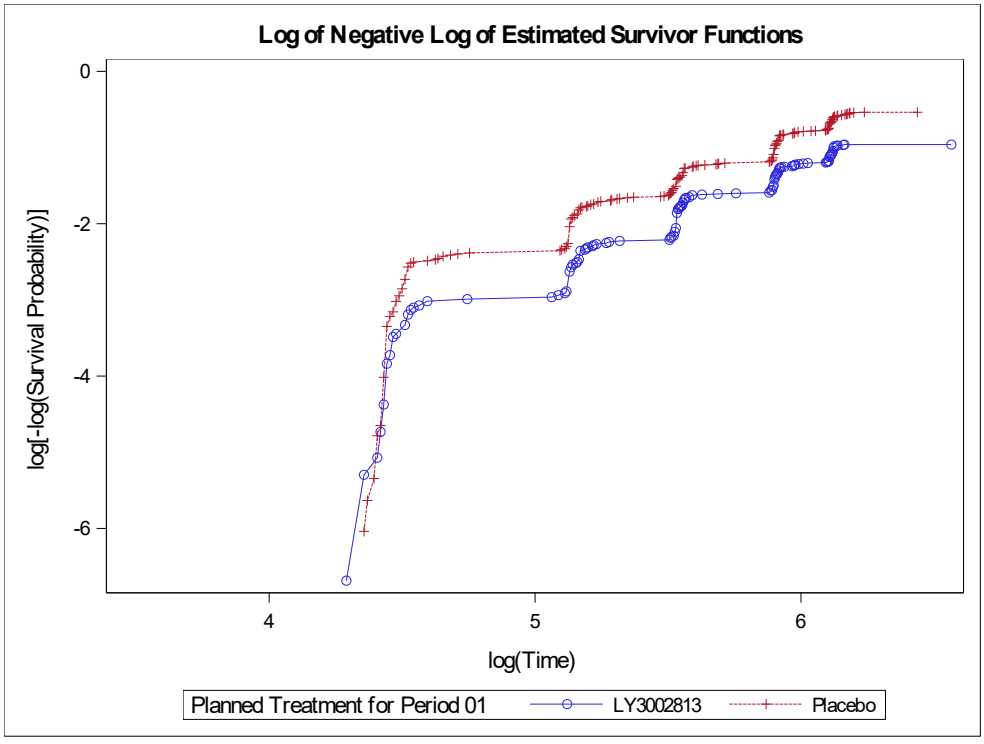
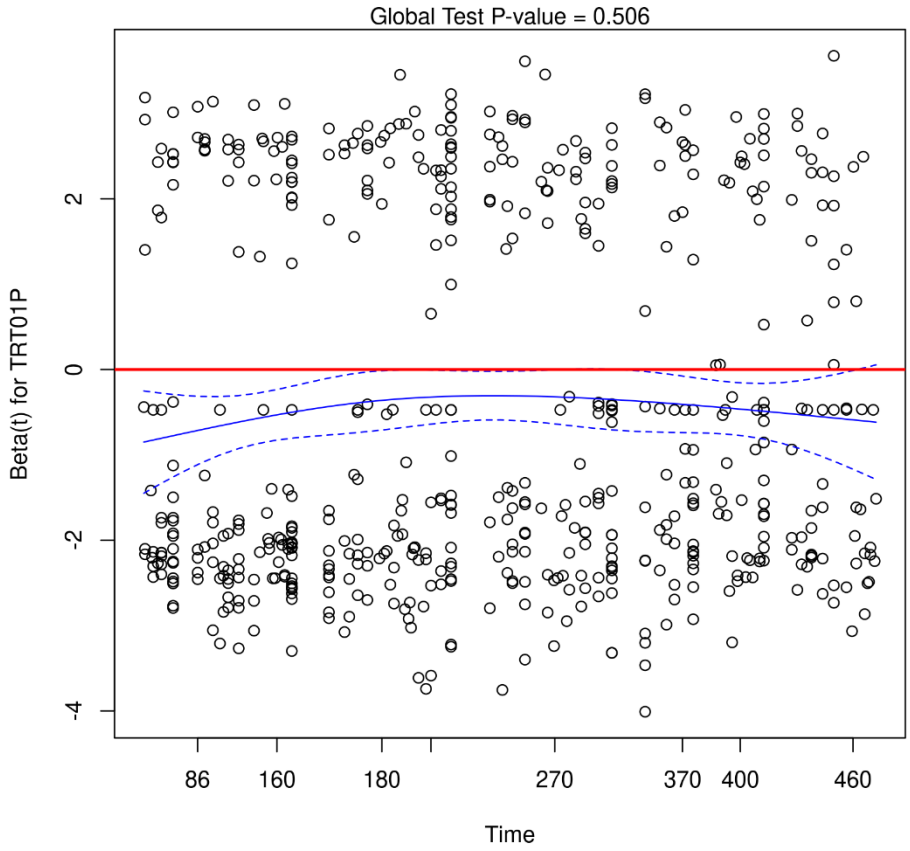


Figure 5: Schoenfeld residuals plot



B8. Priority question: Please clarify what evidence supports the definition of amyloid positivity as amyloid plaque level > 24.1 CL

Within the TRAILBLAZER-ALZ trial program, amyloid clearance was defined as achieving amyloid plaque levels <24.1 centiloids (CL),[41] as measured by amyloid PET, and was consistent with sparse to no neuritic plaques and a visually negative read of the PET scan.

The 24.1 CL value represents the upper limit (95th percentile) of the distribution (mean +1.65 standard deviation) in young controls aged 35 to 55 years (inclusive) and free of cognitive impairment by history and examination,[42] and a CL value less than this value is equivalent to amyloid negative (none or sparse plaques) as verified at autopsy.[41, 43]

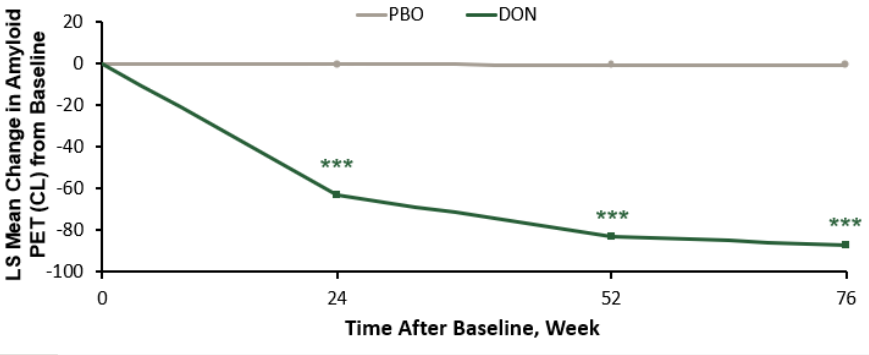
Data from the IDEAS study identified 24.6 CL as the optimal value to discriminate visually positive from negative images.[44] Additionally, Lilly Studies 18F-AV-45-QP01 and QP02 examining the association between visual read and quantification of florbetapir PET in community nuclear medicine physicians showed that a CL value between 24 and 25 best aligned with the visual read positive or negative result.[45]

B9. Priority question: Please provide a graph of the average amyloid levels at different timepoints in the TRAILBLAZER-ALZ 2 trial

The average amyloid levels at different timepoints in the TRAILBLAZER-ALZ 2 trial are

presented in Figure 6.

Figure 6: Mean change in Amyloid PET from baseline (overall population)



					76-week Value, CL	Difference from Baseline, %
PBO, n	812	805	729	690	-0.7	-0.7
DON, n	765	760	670	614	-87.0	-83.7

***p<0.001 vs placebo
Abbreviations: CL: centiloid; DON: donanemab; MMRM: mixed models repeated measures; PET: positron emission tomography; PBO: placebo.
Source: Generated using data from Sims *et al* (2023).[7]

B10. Priority question: On CS page 75, it is stated "Based on amyloid levels at Week 76 in TRAILBLAZER-ALZ 2 and assuming re-accumulation rate of 2.8 CL, the time taken for a return to an amyloid plaque level >24.1 CL, which equates to amyloid positivity, after last treatment is approximately 3.5 years, assuming linear increase over time." Please clarify the estimation of the time needed to return to amyloid positivity after stopping treatment as the previous sentence suggests that the amyloid levels at Week 76 should be around 14.3 CL. However, based on the amyloid plaque level at baseline presented in CS Table 7 (103.5 CL) and the decrease in amyloid plaque level from baseline to week 76 stated in CS page 51 (87 CL), the amyloid levels at week 76 are 16.5 CL.

In order to calculate the time taken to return to a level of 'amyloid positivity', the observed mean amyloid level at week 76 was used rather than the baseline level minus the estimated LS mean change from baseline. These data are available in Table AACI.8.45 in the TRAILBLAZER-ALZ 2 CSR.[1]

The model assumes that treatment effect assessed at 18-months is maintained over time until the point at which amyloid positivity (defined as >24.1 amyloid CL) is reached. There is reason to believe based on the observed data that this could be a conservative approach, as the curves continued to diverge across the pivotal trial at 6, 12, 18 months (as shown in Figure 6 and 7 of the CS) and also TB-ALZ EXT.

B11. For the calculation of the relative dose intensity of donanemab, the model uses the incidence of any ARIA events in the donanemab arm (36.8%) and the resolution time of ARIA edema/effusion events (rather than for any ARIA event) for those receiving donanemab (72.4 days). Please clarify whether it is assumed that the resolution time of ARIA edema/effusion events is a proxy to the resolution time of any ARIA event and, if so, please justify this assumption.

A separate resolution time of ARIA-H was not included within the model as most instances of ARIA-H do not disappear or resolve on MRI. Instead, it can be deemed stable if there are no new microhaemorrhages or no increase in the size/number of areas of cortical superficial siderosis. This is challenging however, as while one MRI could indicate that the existing findings are stable, the subsequent MRI could indicate otherwise. Given the challenges in defining and evaluating resolution of ARIA-H, and given that most ARIA-H in excess of background levels occurs in the setting of ARIA-E, the resolution time of ARIA-E was used.

The trial protocol specified that "*reinitiating IP [investigational product] can be considered after resolution of ARIA-E and stabilisation of ARIA-H imaging findings and the resolution of any associated symptoms*."

It is expected that the time to stabilisation of ARIA-H is likely to be longer than the resolution time for ARIA-E as ARIA-H can continue to evolve after ARIA-E appears. Therefore, the assumption of using mean time to resolution of ARIA-E to calculate relative dose intensity is considered conservative.

B12. The EAG was not able to find the median time in trial prior to placebo switch (47 weeks) for patients who achieved early amyloid clearance at 24 and 52 weeks in the references provided within the company submission (CS page 77). Please clarify which source presents these data.

The value is reported on slide 28 of Sims *et al* (2023a), which is provided in the accompanying reference pack.[46]

B13. Priority question: CS Figure 18 shows the change from baseline to Week 76 in the CDR-SB for patients who discontinued treatment at 6 or 12 months due to amyloid clearance. Please clarify how CS Figure 18 was derived and adapted from the study by Sims et al. 2023.

The change from baseline to Week 76 in the CDR-SB for patients who discontinued treatment at 6 or 12 months due to amyloid clearance value was incorrectly referenced to Sims *et al* (2023), Lilly apologises for this oversight. The value is instead reported in Sims *et al* (2023a), which is provided in the accompanying reference pack.[46]

B14. The EAG was not able to find the proportion of patients stopping treatment at 12 months due to amyloid clearance in the references provided within the company

submission (CS Table 23). Please clarify where in the Sims et al. 2023 study these data are presented.

Table AACI 5.16 in the CSR outlines the number of patients achieving the amyloid clearance criteria for dose cessation at Week 24 and Week 52. This shows that 29.7% of patients had achieved amyloid clearance at Week 24, and 66.1% at Week 52. This equates to an additional 36.4% patients achieving clearance at 12-months, as this is reported cumulatively in the CSR but needs to be modelled at each individual timepoint in the model in the CS.

B15. Priority question: Transition probabilities from the trials

a) Please explain why the transition probabilities between health states used in the economic model were not obtained from the TRAILBLAZER-ALZ trials.

Within the trial, clinical outcome assessments were conducted every 3 months. For the calculation of transition probabilities, similar results indicating the same disease health state were required to ensure stability in estimating progression and reduce potential scale noise. Given the 18-month timeframe of the trial, the data collected are therefore not sensitive enough to accurately inform the transition probabilities. Additionally, as the trial population was primarily made up of patients with MCI due to AD and mild AD dementia, reliable information on the risk of transitioning into more severe health states is not available from the trial.

Therefore, due to the trial design and relatively short timeframe (18 months) of the TRAILBLAZER-ALZ 2 trial, it was not possible to collect reliable long-term data on transition probabilities within the trial.

b) Please add the option to use the transition probabilities from the TRAILBLAZER-ALZ and TRAILBLAZER-ALZ 2 trials in the economic model.

Due to the substantial limitations of using transition probabilities from the TRAILBLAZER-ALZ trials, as described in the response to Part (a) of the question, an updated model has not been provided here.

B16. Priority question: Transition probabilities for natural disease progression

a) Please provide the details (including relevant files and calculations) to derive the transition probabilities for the natural disease progression which are based on the data from the National Alzheimer's Coordinating Centre (NACC) (CS Table 24).

Accurate transition probabilities are essential for the economic modelling of AD, and a study was initiated to generate robust estimates of the annual probabilities of transitioning between various AD health states across the full disease spectrum, based on the publicly available longitudinal data from the NACC Uniform Data Set.

The primary objective of the study was to estimate annual transition probabilities from one disease stage to a more advanced stage among a recent prevalent cohort of participants with biomarker-confirmed early AD. Full details of the study design and statistical methods are available in the study protocol, provided in the reference pack alongside this response.[47] The estimated annual transition probabilities were rescaled to the model cycle to align with the cycle length as follows:

1. The probability of transitioning out of any given state is converted to an exponential rate that is scaled to align with the cycle length.
2. The scaled rates are then reconverted to the probabilities.
3. The probabilities for remaining in the same state (i.e., the probabilities on the principal diagonal of the trace matrix) are calculated as the difference between 100% and the row sums of scaled probabilities in order to ensure that the transition probabilities from each state sum to 100%.

b) What are the criteria and thresholds for patients transitioning from one state to another?

Please see Table 17 below for health state assignments according to CDR-SB, CDR-G and MMSE.

Table 17: Outcome assessment instrument health state assignments

Health state	CDR-SB	CDR-Global	MMSE
Questionable/MCI	0.5-4	0.5 and clinical MCI	≤27[a]
Mild AD	4.5-9	0.5 and clinical dementia OR 1	26-20
Moderate AD	9.5-15.5	2	19-10
Severe AD	16-18	3	9-0

Footnotes: In addition to instrument-assigned health states, participants were also assigned a health state based on a clinician's assessment at the index date. In cases where a participant was assessed as having MCI or dementia by a clinician, but whose scores indicated normal cognition, the least severe possible score consistent with the clinician assessment at their index visit was assigned. For participants assessed as having MCI, the least severe score in the MCI range for each respective instrument was assigned. Similarly, for participants assessed as having dementia, the least severe score in the Mild AD range for each respective instrument was assigned.
[a]There is no established standardised MMSE score for MCI.
Abbreviations: AD: Alzheimer's disease; CDR-SB: Clinical Dementia Rating - Sum of Boxes; MCI: mild cognitive impairment; MMSE: Mini-Mental State Examination.

c) Please comment on the generalisability of using the US NACC analysis population to inform transition probabilities and the treatment of Alzheimer's disease the UK clinical setting, also supporting this with evidence and/or expert opinion.

The NACC, established in 1999, maintains a cumulative database including clinical evaluations, neuropathology data (when available) and MRI imaging. The data are contributed by more than 42 past and present Alzheimer's Disease Research Centres (ADRCs) supported by the U.S. National Institute on Aging/NIH, where all enrolled subjects undergo a standardised evaluation. The UDS reflects the total enrolment at the ADRCs since 2005 (N~50,200) and includes subjects

with a range of cognitive status — normal cognition, MCI, and demented, due to a variety of etiologies including AD. The UDS is longitudinal, and its protocol requires approximately annual follow-up if the subject is able to participate. The UDS contains information about participant demographics, family history, medical history (including medication use), cognitive status (based on validated instruments such as the MMSE and CDR), functional status (evaluated using the Functional Assessment Questionnaire [FAQ]), behavioural symptoms (evaluated using the Neuropsychiatric Inventory Questionnaire [NPI-Q]), clinical diagnoses of cognitive impairment (including consensus-based determinations), as well as detailed information regarding select other conditions. Of particular relevance, starting in 2015, some ADRCs also began collecting information on select biomarkers ante-mortem, including markers of dementia (e.g., abnormally elevated amyloid on PET and abnormally low amyloid in cerebrospinal fluid [CSF]). NACC is therefore the most comprehensive dataset in patients with amyloid positive status capturing transition probabilities across the disease spectrum.

On average, the NACC participants are more educated than the general population (the median years of education in the study was 16 years), which may have some impact on generalisability, as education has been shown to be an independent predictor of disease onset/progression though KOL feedback suggest that the evidence on the impact of education on disease progression is heterogenous and rather related to the timepoint when patients are diagnosed rather than impacting the underlying disease progression. Differences in rates of certain underlying comorbidities could also influence the progression rates (e.g., number of CVD conditions, history of cerebrovascular events), though Lilly would expect the incremental effect to be limited after adjusting for age and sex.

Based on published literature and feedback from KOLs,[48] the key prognostic factors of disease progression in AD are age and sex, which KOL feedback sought by Lilly suggested that age and gender in the NACC data would likely differ from the UK population. The estimated transition probabilities were further adjusted for age and sex given that they are prognostic factors. In addition biomarker status was identified as a prognostic factor,[48] which was accounted for in the patient selection of the analysis population by requiring post- or ante-mortem biomarker information for determining AD aetiology.

Otherwise, KOLs did not believe that other factors would impact disease progression to any meaningful extent. Hence, it is believed that the transition probabilities are generalisable to the UK setting.

Overall, the NACC dataset was chosen because it is a robust sample in the relevant population for the decision problem, and its inclusion of MCI patients means it did not need to be supplemented with additional data from the literature, thereby reducing uncertainty in the model.

d) Please comment on alternative datasets and approaches being used for the modelling of AD in the models that were compared in the Handels et al. 2022 article, also referenced by the company.

Different sources that could be used to inform transition probabilities in the model were explored. For instance, Wimo *et al*. 2020 provided transition probabilities based on a Swedish dementia registry starting from 2007.[49] The natural progression rates were estimated based on 53,880 persons with AD dementia staged per MMSE (mild: 21–30, moderate: 10–20, severe 0–9). Because the analysis grouped MMSE 21–30 together, there was no transition probability specific

to MCI due to AD. Vos et al. 2015 reported a three-year progression risk of 50% per the International Working Group-1 (IWG-1) diagnostic criteria based on their review of 1,607 patients with MCI in multiple centres.[50] Therefore, assuming a constant hazard, an annual transition rate can be derived from MCI due to AD to mild AD dementia (20.6%), which can be applied assuming no transition to other AD dementia stages. The AD dementia patients included in the analysis of the Swedish dementia registry database did not have amyloid beta status confirmed.

The EU-GERAS study,[51] a prospective observational study conducted in the UK, Germany and France was also explored for transition probabilities. However, patients didn't require amyloid confirmation to participate in this study and patients with MCI due to AD dementia were not enrolled into this study, which requires the transition probabilities to be supplemented by the literature and therefore additional assumptions. None of the studies included the CDR, hence no transition probabilities could be estimated increasing uncertainty in the model due to the inconsistencies in the scales for key parameters.

Transition probabilities based on TRAILBLAZER-ALZ 2 were also explored. Please see question B15a for further rationale on why it was not further considered for estimating transition probabilities.

B17. Priority question: Mortality hazard ratio

a) Please clarify how the hazard ratio for mortality (2.55) was derived from the source (Office of National Statistics 2023).

The hazard ratio (HR) for mortality was calculated by the Office of National Statistics (ONS).[52] The 2.55 value is the adjusted hazard ratio for deaths not involving COVID-19 amongst males aged 65 years and over, comparing people with dementia to people without dementia (reference group) in England from 24 January 2020 to 31 December 2022. The model was adjusted for age, ethnicity, geography, socio-economic status, education, health conditions, harmful drinking behaviour, frailty, care home status, and considered only deaths not involving COVID-19. The ONS is the UK's largest independent producer of official statistics and its recognised national statistical institute. Therefore, dementia-related mortality data from the ONS was deemed to be relevant and appropriate for inclusion in the economic model.

The male HR was used as it was higher than the observed HR for females; the further possible refinement of applying a weighted average HR incorporating both male and female HRs was considered to have been immaterial to the base case ICER.

b) Please change the model so that it is possible to vary the mortality hazard ratio by severity of Alzheimer's disease (mild, moderate, severe).

The approach to mortality in economic modelling of Alzheimer's Disease is a well-established challenge.[53] Various approaches are possible, but it is important to understand the implications of the selected approach in terms of predictions that are being made about the implicit survival benefit of disease-modifying therapies. It is challenging to make predictions about the long -term impact of slowing disease progression on mortality, due to confounding factors impacting mortality in later stages of disease. For example, increased levels of care for community and

residential patients in late stages of AD dementia can mean that they have fewer falls, improved medication adherence, and may be provided with regular meals – all of which can (counter-intuitively) reduce the risk of mortality as patients progress.

When modelling any mortality benefit, the stage at which the benefit occurs will impact the ICER. If mortality benefit is observed at the later stages of disease, then the ICER will increase due to higher costs of care and low utilities. Modelling the mortality benefit at the earlier stages of disease will result in a lower ICER due to higher QALY's. If mortality benefit is similar across all health care states, then the impact on the ICER is neutral due to the higher QALY's balancing the increased costs.

When an increasing mortality risk with more severe health states is applied, a treatment which slows disease progression results in an indirect mortality benefit, which is highest during the more severe health states. This has a negative effect on the ICER due to the high care costs associated with these health states.

The base-case model did not include the option to vary the mortality HR by severity of AD, due to the assumptions implicit with this option. By varying the mortality HR by AD disease stage, this implicitly assumes a survival benefit with donanemab as treatment with donanemab prolongs the time a patient stays in the earlier health states. As there are not currently data to support a potential survival benefit, such an assumption is associated with considerable uncertainty.

The model has been updated to include the option to vary the mortality HR by severity of AD, to enable the EAG to investigate the impact of such assumptions on the cost-effectiveness results. HRs for the different health states were informed by the NACC analysis that was used to inform the transition probabilities within the model (and that is described in further detail in response to Question B16). Parametric regression models were used to estimate AD health-state specific hazard ratios for death relative to MCI as the reference category. Participant age in years at the event-time was used as the time scale. To account for censoring in real-world situations, participant follow-up was censored 1 year after the last available visit with a measured health state. The study population used for the exploratory analyses is the same as the cohort for estimating the transition probabilities. The model estimated the hazard ratios by assuming a Weibull distribution for participant survival times.

Specifically, a proportional hazards parametrization was used, with probability density function of the Weibull distribution given by:

$f(t)= p\lambda t^{(p-1)} e^{(-\lambda t^p)}$

where $p>0$, is the Weibull shape parameter and $\lambda>0$, is the event rate parameter, and the hazard function can be expressed as:

$h(t)= p\lambda t^{(p-1)}$

Based on this parametrization, the hazard ratio for two health states A and B (e.g., MCI and severe AD) is given by:

$\theta(t)=p_A \lambda_A p_B \lambda_B t^{(p_A-p_B)}$

and under the assumption of proportionality of hazards, $\theta=\lambda_A/\lambda B$.

The model was estimated using the maximum likelihood approach. For each of the estimated hazard ratios, 95% CIs and p-values were reported. The analysis was conducted in a prevalent sample in participants aged 60 years and over at index date to align with the inclusion criteria in AACI. Estimates were produced using the health state definitions based on CDR-SB, which is in line with the used transition probabilities estimates in the model.

The hazard ratios used are detailed in Table 18 and the results of the scenario are presented in Table 19. However, Lilly maintain that the original approach to modelling mortality was appropriate and as such, have not updated the base case assumptions to include differential mortality risk by stages of AD.

Table 18: Mortality risk for patients with AD (60+ years of age) compared to general population

Health state	Risk of mortality; HR (95% CI)
MCI due to AD	1
Mild AD dementia	1.79 (1.54, 2.09)
Moderate AD dementia	1.75 (1.42; 2.14)
Severe AD dementia	3.41 (2.87, 4.07)

Abbreviations: AD: Alzheimer's Disease; MCI: mild cognitive impairment.
Source: Eli Lilly Data on File: NACC Survival Analysis: Hazards of Death by Health State.

Table 19: Scenario analyses (donanemab PAS price) – inclusion of a variable mortality hazard ratio

Technologies	Inc. costs (£)	Inc. QALYs	ICER (£/QALY)
Original base case (severity modifier)	£13,953.18	0.85	£16,466.70
Original base case (no severity modifier)	£13,953.18	0.71	£19,736.03
Inclusion of a variable mortality hazard ratio (severity modifier)	£21,663.43	0.87	£24,849.77
Inclusion of a variable mortality hazard ratio (no severity modifier)	£21,663.43	0.73	£29,819.72

Abbreviations: ICER: incremental cost-effectiveness ratio; Inc. incremental; PAS:; patient access scheme; QALY: quality-adjusted life year.

B18. Priority question: Please clarify how the mortality risk associated with donanemab treatment (0.35%) was derived from the indicated source (Sims et al. 2023) (CS section B.3.2.5).

The mortality risk associated with donanemab was calculated using the total deaths considered related to treatment within the TRAILBLAZER-ALZ 2 trial (3) divided by the total number of trial participants (853). The resulting value (0.003516) was then converted into a percentage.

B19. Please clarify how the adverse event incidence of injection-related reactions and hypersensitivity was derived from the TRAILBLAZER ALZ-2 trial (CS B.3.2.4 Table 28)

Treatment-emergent adverse events (TEAE) were used to inform these parameters, defined as an event that first occurred or worsened after the treatment initiation date and up to either the

first visit date of long term extension phase (LTE) - 1 day or end of treatment period in double blinded phase + 57 days, whichever occurs first.

Based on Table 8.176 in the CSR, there were 29 moderate and 3 severe cases of IRR among 853 donanemab treated patients. There were 5 moderate and 2 severe cases of hypersensitivity among 853 donanemab treated patients.

Health-related quality of life

B20. For the calculation of the disutility for anaphylactic reaction, please clarify why you apply the 15% reduction in baseline utility of caregivers rather than patients (CS Table 30 and model cell Utility!L68)

Lilly can confirm that this is an input error within the model and agree with the EAG that the 15% reduction should be applied in baseline utility of patients but not caregivers. This has now been corrected within the model. Following the correction, the disutility for anaphylactic reaction changed from -0.018 to -0.012, the impact on the ICER is minimal.

B21. Priority question: Please explain why the patient utilities for MCI due to AD and mild AD dementia were assumed to be the same whether patients were cared for in the community or a residential care setting (CS Table 31).

Lilly maintain that there is no reason that the patient utilities would differ for any of the health states in community or residential settings. There is also a lack of granular data available to sufficiently inform different patient utility values between community and residential settings for each disease state. The patient utility values were therefore assumed to be the same for each setting.

a) **Please explain why the patient undiscounted life years were assumed to be different depending on whether they were cared for in the community or a residential care setting (CS Table 44).**

Patients will spend a different amount of time being cared for in the community and residential care settings, even if the utility values for each setting are assumed to be equal. As a result, the undiscounted life years would also be different for each setting.

B22. Priority question: Please explain why the child/spouse carer utilities for MCI due to AD and mild AD dementia were assumed to be the same whether patients were cared for in the community or a residential care setting (CS Table 31). Please provide the full results of the primary vignette study (CS Table 32).

There are very few patients with MCI due to AD and mild AD dementia expected to move into the residential care setting. According to KOL feedback, these patients are likely moving into the residential care setting due to factors outside of those caused by their AD.[54] As a result, the

child/spouse carer utilities for MCI due to AD and mild AD dementia were assumed to be the same across both settings.

Results of the primary vignette study

The primary vignette-based time trade-off (TTO) utility study was conducted with a sample of general population participants in the United Kingdom and replicated in the United States. Each participant attended one in-person interview session during which they valued six health states. Health states began with a description of a relative (either a parent or a spouse/partner) with varying severity levels of MCI and AD. After describing the patient, health states continued with a description of the caregiver's responsibilities and impacts.

A total of 304 valid interviews were conducted in the UK and 202 valid interviews in the US. Mean time trade-off utilities scores in the UK presented in Table 20 and a comparison of the scores between the UK and US is presented in Table 21.

Table 20. Utility scores in the UK, Total Sample (N=304)

Health State	N	Mean	SD	Range	95% CI
Parent caregiver health states					
MCI	304	0.843	0.176	-0.075 – 1.000	0.823 – 0.862
Mild AD	304	0.775	0.198	-0.125 – 1.000	0.752 – 0.797
Moderate AD	304	0.615	0.321	-0.900 – 0.975	0.579 – 0.652
Spouse caregiver health states					
MCI	304	0.818	0.184	-0.075 – 1.000	0.797 – 0.838
Mild AD	304	0.715	0.246	-0.725 – 1.000	0.687 – 0.742
Moderate AD	304	0.542	0.343	-0.825 – 0.975	0.503 – 0.580

Footnotes: TTO scores are on a scale anchored with 0 representing dead and 1 representing full health (no caregiving responsibilities). A utility of -1.000 or -0.975 is at the floor. A utility of 1.000 or 0.975 is at the ceiling.
Abbreviations: AD: Alzheimer's Disease; CI: confidence interval; MCI: mild cognitive impairment; SD: standard deviation; TTO: time trade off.

Table 21. Comparison of UK and US utility scores

Health State	UK (N=304)		US (N=202)	
	Mean	SD	Mean	SD
Parent caregiver health states				
MCI	0.84	0.18	0.85	0.20
Mild AD	0.77	0.20	0.77	0.28
Moderate AD	0.62	0.32	0.65	0.34
Spouse caregiver health states				
MCI	0.82	0.18	0.84	0.20
Mild AD	0.71	0.25	0.74	0.30
Moderate AD	0.54	0.34	0.59	0.40

Abbreviations: AD: Alzheimer's Disease; CI: confidence interval; MCI: mild cognitive impairment; SD: standard deviation.

B23. Priority question: On CS page 87, it is stated that an adjustment was made to derive the caregiver utilities for the severe AD dementia health states. Please give the full details of this adjustment and explain how the values in CS

Table 32 for severe AD dementia in the community setting were derived from the vignette studies.

As discussed in Section B.3.3.5 of Document B, a second vignette study (for which, data collection took place in Q1 2016) was used to inform the severe health state in the community setting in the model. The severe health state was not included in the most recent (primary) vignette study to ensure that participants were not overwhelmed by the number of time trade-off exercises that they were asked to complete. The severe utility score for caregivers living with the patient in community setting (0.49) from the second study was adjusted for the difference observed between the moderate health states (previous study: 0.65) of this and the primary vignette studies (parent relationship: 0.615, spouse: 0.542).

This adjustment was done to ensure consistency and that factors that may have impacted HRQoL of informal caregivers differently between the studies (e.g., the COVID-19 pandemic or overall economic situation) were accounted for within the analysis, given the time gap between the studies.

Resource use and costs

B24. The EAG notes that costs for the MCI due to AD health state differ between CS Table 39 and 40, even though they are taken from the same source. Please explain the reason for the difference in these two costs.

Lilly can confirm that this is an error in Table 40 within the submission. The MCI due to AD health state cost in Table 40 should be £1,385.75 rather than £1,475.45, as reported. This error was not replicated within the model and as such, this had no impact on the cost-effectiveness results.

a) Please explain what the footnote under Table 40, footnote: '*Includes health and social care costs' is referring to – is it all rows of Table 40 or only some?

The footnote 'includes health and social care costs' refers to all rows within Table 40.

b) Please clarify whether Table 39 and 40, which are referred to as including health and social care costs, include direct medical and direct non-medical costs for each severity level, or as indicated for the same values in Table 47 'Direct medical annual costs' only?

This is a labelling error in Table 47, as the costs listed as 'Direct medical annual costs' do include both health and social care costs. The labelling in Tables 39 and 40 of the CS is correct.

B25. Priority question: Please add to the model the facility to include costs for one or more outpatient consultant visit per cycle during the treatment period.

The NHS Reference Costs are considered to be a comprehensive source of resource costs, and costs for PET scan and MRI scans should therefore include the extent of the visit, performance

of the scan, and reading of the results. As such, Lilly maintain that the cost of outpatient consultant visits are covered by the NHS Reference Costs included within the model. However, to investigate the uncertainty associated with this assumption, a scenario analysis has been conducted in which the cost of one outpatient consultant visit (NHS Cost Service Code 400: ; Consultant-Led Neurology Outpatient Visit) is modelled per cycle for all patients remaining on donanemab treatment. The results of this scenario analysis are presented in Table 22 and demonstrate that this assumption has a minimal impact on the ICER.

Table 22: Scenario analyses (donanemab PAS price) – inclusion of the cost of an outpatient consultant visit

Technologies	Inc. costs (£)	Inc. QALYs	ICER (£/QALY)
Original base case (severity modifier)	£13,953.18	0.85	£16,466.70
Original base case (no severity modifier)	£13,953.18	0.71	£19,736.03
Inclusion of the cost of an outpatient consultant visit (severity modifier)	£14,486.54	0.85	£17,075.37
Inclusion of the cost of an outpatient consultant visit (no severity modifier)	£14,486.54	0.71	£20,490.44

Abbreviations: ICER: incremental cost-effectiveness ratio; Inc. incremental; PAS: patient access scheme; QALY: quality-adjusted life year.

B26. PRIORITY QUESTION Treatment with donanemab is conditional upon confirmation of amyloid beta (Aβ) pathology. In the TRAILBLAZER-ALZ 2 trial, ~20% of the people screened were randomised into the trial and a similar proportion were excluded due to low amyloid pathology. Diagnostic testing costs are included in the CS base-case for testing with amyloid PET of CSF. The screening population in the UK is estimated to be around 283k people, consisting of people with MCI due to AD or mild dementia due to AD (see https://www.nice.org.uk/Media/Default/About/what-we-do/HTA%20Lab/Appendix-D.pdf). Although other factors would impact the need to be screened, such as the presence of comorbidities and the willingness to undergo testing, the cost of testing for those that are not amyloid positive should be incorporated.

a) **Footer to Table 38 notes that a factor of 2 is applied to proportions having CSF and PET scanned to account for patients who receive a diagnostic test but do not go on to receive treatment with donanemab (and a factor of 4 is explored in scenario analysis). Please provide a justification for the base-case assumption that the proportion who are**

screened and ultimately not eligible for donanemab is the same as the number who do receive donanemab.

Within the framework of a cost-effectiveness model, the cost of diagnostic testing needs to be in the form of the number of screening tests undertaken to identify one eligible patient. In the base case analysis, it was assumed that two people would need to be tested for amyloid positivity to identify one eligible patient. This assumption was derived from clinical expert opinion and is predicated on the assumption that a full diagnostic workup would be carried out ahead of the costly, amyloid positivity screening. Based on published literature by Jansen et al (2022); the rate of amyloid positivity in a large study (~19,000 patients) was found to be ~51% in MCI patients and 79-87% for Mild AD (confirmed by CSF or amyloid PET). This study confirms KOL expectation that the need to test more than two people to identify one eligible patient is unlikely.[55]

b) Please provide an updated economic model which incorporates diagnostic testing costs for all people eligible for screening into the costs for donanemab.

As noted in the response to part (a), it is not possible to implement this scenario within a cost-effectiveness framework due to the form required for costs of diagnostic testing. However, in order to investigate the impact of this assumption on the cost-effectiveness results, multiple scenario analyses were presented within the CS. These analyses demonstrated that, even when the number of diagnostic tests required to identify one patient was doubled, the results of donanemab versus established clinical management without donanemab for patients with MCI due to AD and Mild AD dementia fell comfortably under the £30,000 willingness-to-pay threshold.

An updated economic model incorporating the diagnostic testing costs for all people eligible for screening has therefore not been provided.

c) Please include a scenario which includes the costs of referral to local services for people that are not amyloid positive.

As per the NICE perspective, costs incurred by patients who do not receive donanemab are not relevant to the scope of this appraisal. Instead, only the costs of screening those who would be screened but who test negative for presence of amyloid are to be included under the NICE perspective. As noted in the response to part (a), these costs have already been included within the cost-effectiveness model and as such, no further scenarios have been presented.

d) Please include scenarios for future retesting those who are initially excluded due to low amyloid pathology.

The cost of screen failures have already been included in the overall screen failure rate applied within the model and as such, the base case already includes the costs of those who will never screen positive and those who may in theory later screen positive. Therefore, no further scenarios have been presented.

e) **Is the potential for future re-treatment expected to be included or excluded from the marketing authorisation for donanemab (or not considered)? It is expected that people who have previously had donanemab would be screened for amyloid after stopping and potentially retreated in the future?**

It is not anticipated that the marketing authorisation for donanemab would include retreatment with donanemab for people who had previously received donanemab. It is therefore not expected that these patients would be re-screened for amyloid positivity following treatment discontinuation.

B27. Please explain how the Amyloid PET scan 'tracer' costs have been estimated (CS Table 37)

[redacted]

B28. PRIORITY QUESTION In TRAILBLAZER-ALZ 2, APOE4 carrier assessment was conducted at screening.

a) **Is *APOE4* testing expected to be a requirement of the marketing authorisation for donanemab?**

[redacted]

Most serious ARIA events occurred within 12 weeks of initiation of treatment and an additional MRI prior to the third dose may aid in earlier detection of ARIA, particularly for patients with ARIA risk factors such as apolipoprotein E ε4 allele (APOE ε4) carriers, baseline cerebral microhaemorrhages and superficial siderosis.

b) **If not a requirement of the marketing authorisation, what proportion of people are expected to receive *APOE4* tests in UK clinical practice?**

It is assumed that within clinical practice, 100% of patients would receive APOE4 testing, in order to inform risk of ARIA. As such, within the economic model, the cost of an APOE4 test is applied for 100% of patients.

c) Please conduct a scenario including the costs of *APOE4* testing, including the cost of the test itself, outpatient appointment to receive the test and genetic counselling?

In the context of initiating treatment with donanemab, APOE4 testing is not a diagnostic, but instead used to appropriately define and manage the risk factors for ARIA for patients.

The cost of the APOE4 testing itself has been provided within the economic model, as described in Section B.3.4.2 of Document B. However, genetic counselling is not considered to be appropriate within this setting as patients will have already been diagnosed with AD at the stage of treatment initiation. Based on these two points, it was not considered relevant to present further scenarios investigating this point.

d) Is it expected that the monitoring requirements (for example, number of MRI scans) will be different for people who are *APOE4* carriers? If so, please conduct scenarios exploring this.

[redacted]

A scenario analysis has been conducted assuming one additional MRI scan is conducted for people who are APOE4 carriers. The results of this scenario analysis are presented in Table 23 and demonstrate that this assumption has a minimal impact on the ICER.

Table 23: Scenario analyses (donanemab PAS price) – additional MRI monitoring scan

Technologies	Inc. costs (£)	Inc. QALYs	ICER (£/QALY)
Original base case (severity modifier)	£13,953.18	0.85	£16,466.70
Original base case (no severity modifier)	£13,953.18	0.71	£19,736.03
Inclusion of the cost of an outpatient consultant visit (severity modifier)	£14,150.52	0..85	£16,679.30
Inclusion of the cost of an outpatient consultant visit (no severity modifier)	£14,486.54	0.71	£20,015.16

Abbreviations: ICER: incremental cost-effectiveness ratio; Inc. incremental; PAS: patient access scheme; QALY: quality-adjusted life year.

B29. The model assumes that all patients are required to have received a recent MRI (within 1 year) before initiating treatment with donanemab. This is also an anticipated requirement of the marketing authorisation for donanemab. The model assumed 25% of people will already have had an MRI within the past year, so the cost of 75% of people needing an MRI is modelled. Please provide a justification for the assumption 25% of people will already have had an MRI within the past year.

This assumption is based on KOL feedback that approximately 25% of people identified as eligible for donanemab would likely have had an MRI within the past year. A scenario is presented, assuming no patients have an available MRI within the past year. The results of this scenario analysis are presented in Table 24 and demonstrate that this assumption has a minimal impact on the ICER.

Table 24: Scenario analyses (donanemab PAS price) – 100% MRI required at initiation

Technologies	Inc. costs (£)	Inc. QALYs	ICER (£/QALY)
Original base case (severity modifier)	£13,953.18	0.85	£16,466.70
Original base case (no severity modifier)	£13,953.18	0.71	£19,736.03
100% MRI required at initiation (severity modifier)	£14,002.52	0.85	£16,504.85
100% MRI required at initiation (no severity modifier)	£14,002.52	0.71	£19,805.82

Abbreviations: ICER: incremental cost-effectiveness ratio; Inc. incremental; PAS:; patient access scheme; QALY: quality-adjusted life year.

Results and sensitivity analyses

B30. Priority question: The company scenario analyses (CS Table 51) were run probabilistically. Please state the number of iterations used for each of the scenarios. Is it possible to run the scenarios deterministically in the model?

Probabilistic scenario analyses were run with 2,000 iterations for each scenario. It is possible to run scenarios deterministically within the model. However, in accordance with NICE recommendations, probabilistic scenarios were presented within the CS.[56]

B31. The EAG is not able to replicate the results for scenario 5 (Treat to clear only) and therefore the results obtained when we ran this scenario was different from the results showed in CS Table 51. Please double check whether the results in CS Table 51 are correct.

Lilly agree that the result does not appear to be correct in the original company submission. This scenario is run by setting "% Patients Screened for Amyloid Clearance" to 100% on the Settings sheet within the model. Scenario results are shown below in Table 25.

Table 25: Scenario analyses (donanemab PAS price) – Treat to clear only

Technologies	Inc. costs (£)	Inc. QALYs	ICER (£/QALY)
Original base case (severity modifier)	£13,953.18	0.85	£16,466.70
Original base case (no severity modifier)	£13,953.18	0.71	£19,736.03
Treat to clear only (severity modifier)	£10,045.31	0.85	£11,840.47
Treat to clear only (no severity modifier)	£10,045.31	0.71	£14,208.56

Abbreviations: ICER: incremental cost-effectiveness ratio; Inc. incremental; PAS:; patient access scheme; QALY: quality-adjusted life year.

B32. Priority question: Please provide instructions on how to run scenario 8 (Blood based biomarker test becomes available rule in).

Lilly agree that the result does not appear to be correct in the original company submission. This scenario is run by setting "Distribution of Diagnostic Testing Resources" to 0% on the Resource Utilization Costs sheet for Amyloid PET Scan and CSF and to 100% for Blood-Based Biomarkers. Scenario results are shown below in Table 26.

Table 26: Scenario analyses (donanemab PAS price) – Blood test for rule-in becomes available

Technologies	Inc. costs (£)	Inc. QALYs	ICER (£/QALY)
Original base case (severity modifier)	£13,953.18	0.85	£16,466.70
Original base case (no severity modifier)	£13,953.18	0.71	£19,736.03
Blood test for rule-in becomes available (severity modifier)	£10,045.31	0.85	£11,840.47
Blood test for rule-in becomes available (no severity modifier)	£10,045.31	0.71	£14,208.56

Abbreviations: ICER: incremental cost-effectiveness ratio; Inc. incremental; PAS:; patient access scheme; QALY: quality-adjusted life year.

B33. Priority question: Please provide further details on the assumptions used to estimate the QALY shortfall in CS section B.3.5, including why the total QALYs in CS Table 45 do not match those for the BSC arm in CS Table 49. Please note that carer quality of life, if included in the estimated QALYs for current NHS care, should be excluded from the calculation of absolute and proportional QALY shortfall (please refer to DSU Technical support document 23 [Wailoo 2024]).

As NICE DSU TSD 23 was circulated to the DSU mailing list on the 7th February 2024, after the date of the CS to NICE, Lilly did not to refer to the document during the development of the CS. However, Lilly acknowledge that NICE DSU TSD 23 specifies that carer quality of life should be excluded from the calculation of absolute and proportional QALY shortfall.

Excluding carer quality of life, donanemab does not meet the criteria for a severity modifier. The base case results have therefore been rerun excluding the 1.2x severity multiplier that was included within the CS and are presented in Table 27.

Table 27: Scenario analyses (donanemab PAS price) - exclusion of 1.2x severity multiplier

Technologies	Inc. costs (£)	Inc. QALYs	ICER (£/QALY)
Original base case (Severity Modifier)	£13,953.18	0.85	£16,466.70
Original base case (No Severity Modifier)	£13,953.18	0.71	£19,736.03
Exclusion of 1.2x severity multiplier	£13,953.18	0.71	£19,736.03

Abbreviations: ICER: incremental cost-effectiveness ratio; Inc. incremental; PAS:; patient access scheme; QALY: quality-adjusted life year.

Lilly would like to highlight the disconnect between NICE's stated reference case perspective, including both patient and caregiver QALYs, and the calculation of the severity modifier. The approach recommended in NICE DSU TSD 23 gives no consideration to the profound impact of the condition on caregiver quality of life, highlighted in the caregiver utility study conducted for this appraisal (described in further detail in Section B.3.3.5 of Document B).

Validation

B34. Please explain why amyloid monitoring detection costs are only applied for the first two cycles of the model (see company model sheet Engine!EF54:ef55) and not applied in the third cycle of the model. Please correct the model if this is a technical error.

Amyloid monitoring would only be conducted at 6-months and 12-months, as all patients complete treatment at 18-months (whether treat-to-clear or fixed duration), so no PET scan at 18-months is required.

B35. Priority question: Please provide a validation of the model results compared to the trial for disease progression (by AD health state), for example compared against CS Figure 7.

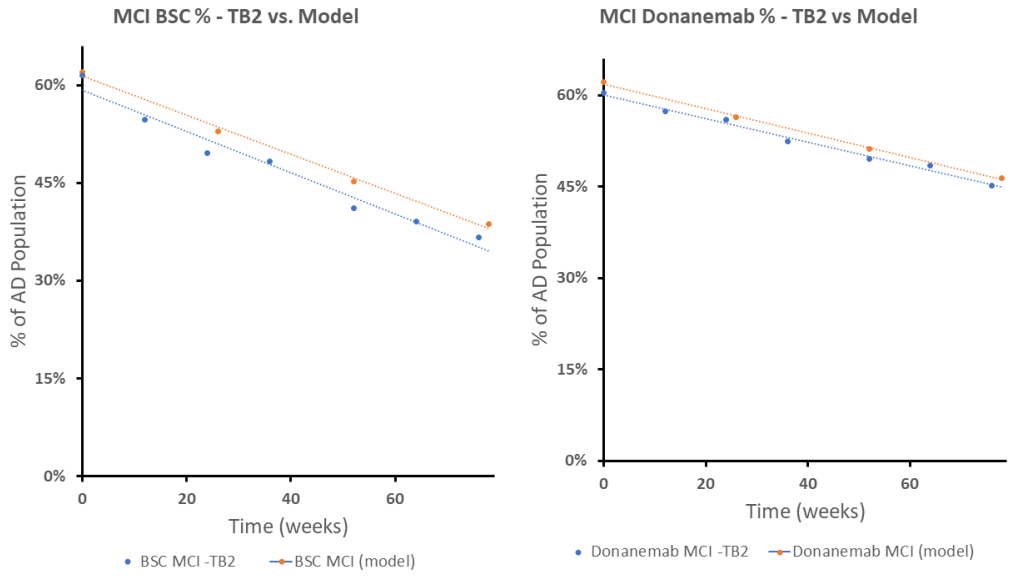
Percentages from TRAILBLAZER-ALZ 2 data and from the model are provided below for each of the health states in the model . It is very important when interpreting these to recall that the model baseline distribution and relative treatment effect are based on the trial but that the model transition probabilities are based on the NACC data, not the trial (the reason for this is discussed further in the response to Question B15 above); as such, it is not expected that the absolute model state occupancies will be aligned with those observed in the trial.

MCI due to AD

The model closely reproduces the trial based distribution of the MCI due to AD health state over time, for both BSC and donanemab. The model outputs show that slightly more patients remain in the MCI due to AD health state at 1.5 years (+2% BSC, +1% Donanemab) than the trial data

indicates.

Figure 7: Comparison of the distribution of the MCI due to AD health state in the model and the TRAILBLAZER-ALZ 2 trial

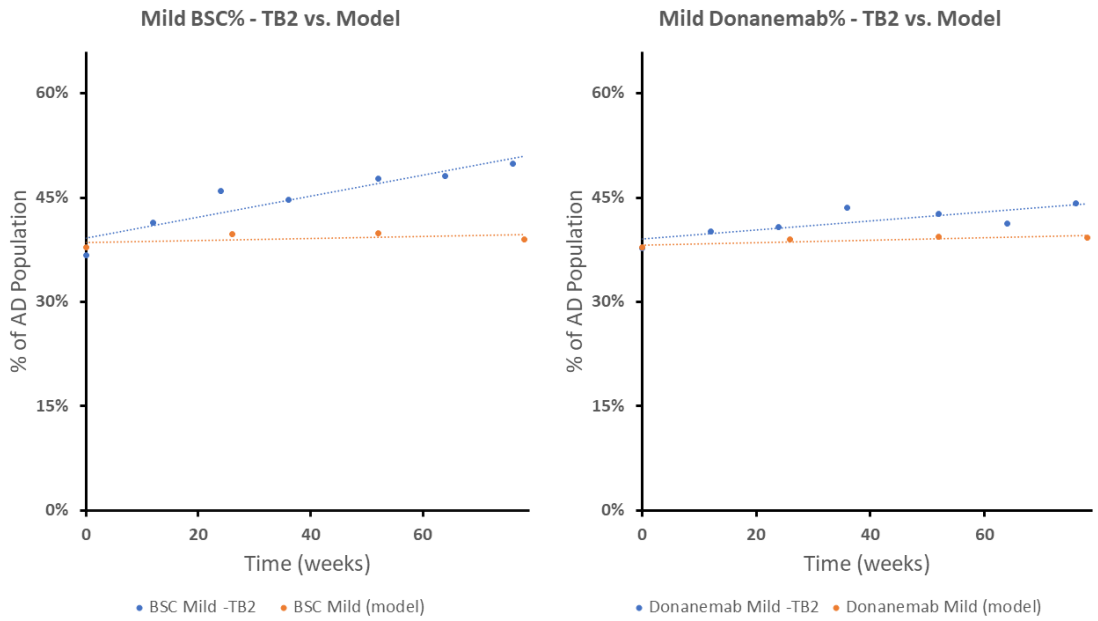


Abbreviations: AD: Alzheimer's Disease; BSC: best supportive care; MCI: mild cognitive impairment; TB2: TRAILBLAZER-ALZ 2.

Mild AD dementia

In the mild health state, patients can come from the MCI health state and move to the moderate health state. The model assigns at 18 months a smaller percentage of patients to the mild AD dementia health state for both BSC and donanemab (Figure 8) indicating that there are more movements in the model than in TB2 data and that the NAAC data for mild patients may result in slightly faster progression. The discrepancy between the model prediction and the trial data at 1.5 years is greater for BSC (−11%) than for donanemab (−5%).

Figure 8: Comparison of the distribution of the mild AD dementia health state in the model and the TRAILBLAZER-ALZ 2 trial

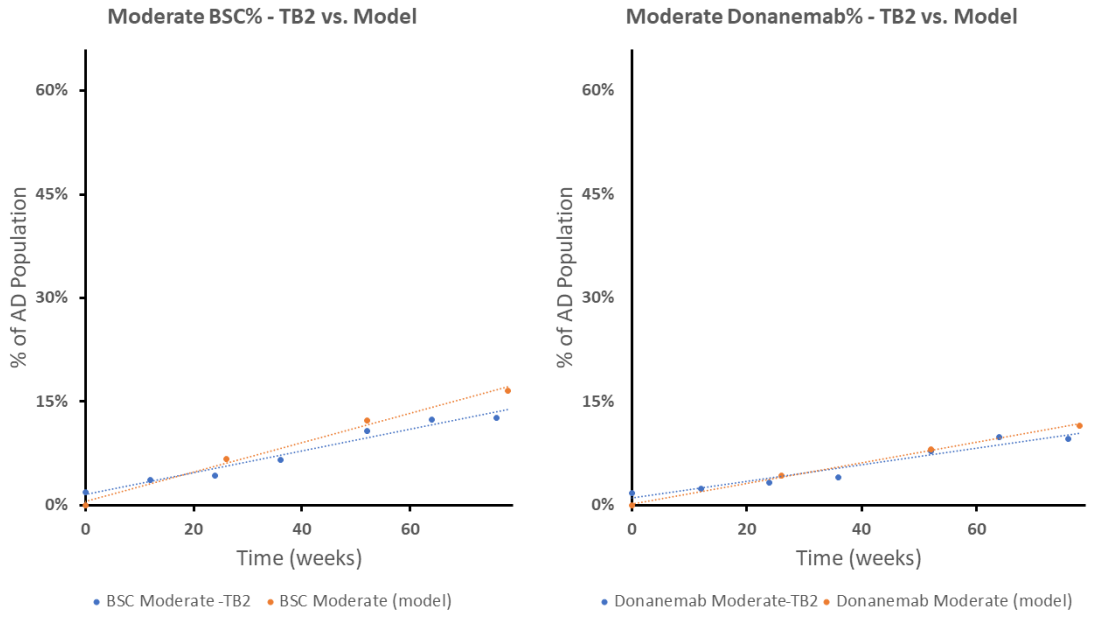


Abbreviations: AD: Alzheimer's Disease; BSC: best supportive care; TB2: TRAILBLAZER-ALZ 2.

Moderate AD dementia

The model closely reproduces the trial based distribution of the moderate AD dementia health state over time, for BSC and donanemab (Figure 9). The discrepancy between the model prediction and the trial data at 1.5 years is greater for BSC (+4%) than for donanemab (+2%).

Figure 9: Comparison of the distribution of the moderate AD dementia health state in the model and the TRAILBLAZER-ALZ 2 trial

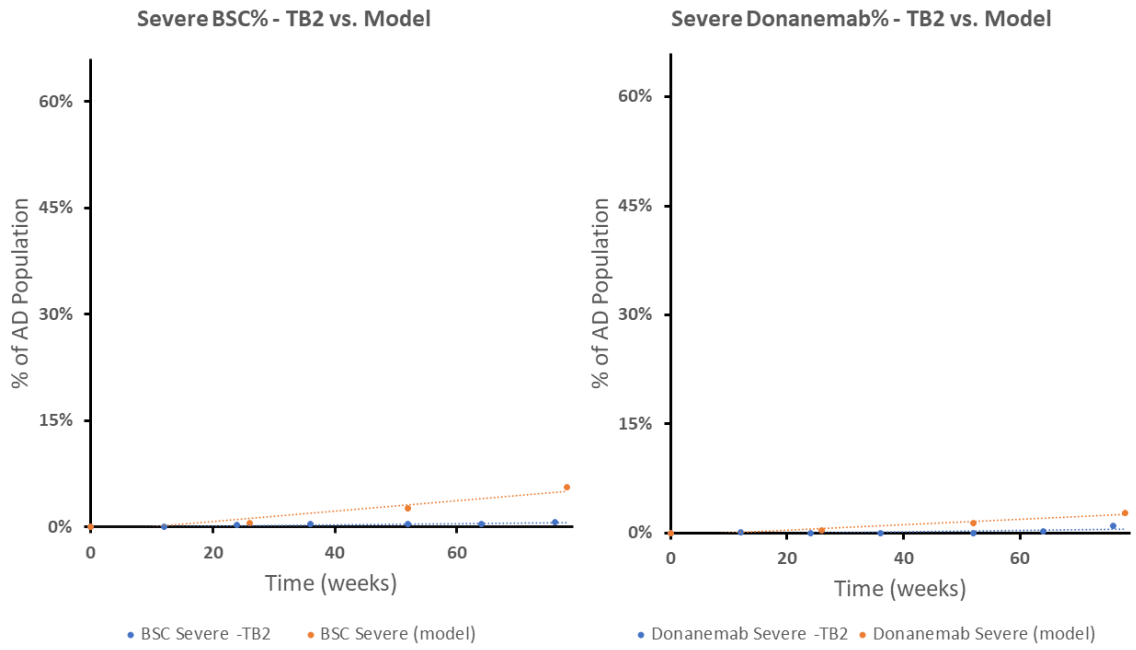


Abbreviations: AD: Alzheimer's Disease; BSC: best supportive care; TB2: TRAILBLAZER-ALZ 2.

Severe AD dementia

The model assigns slightly more patients to the severe AD dementia health state than indicated by the trial data (Figure 10). The trial data does not show a clear difference between donanemab and BSC (based on very small sample sizes (6 patients in donanemab and 7 patients in BSC); however, the model indicates faster growth into the severe AD dementia health state for both donanemab and BSC. The discrepancy between the model prediction and the trial data at 1.5 years is greater for BSC (+5.5%) than for donanemab (+2.5%). However, this needs to be interpreted with caution given the trial population (ie. early symptomatic AD), the trial design and relatively short timeframe (18 months) of the TRAILBLAZER-ALZ 2 trial, it was not possible to collect reliable long-term data in more severe health states (see also question B15).

Figure 10: Comparison of the distribution of the severe AD dementia health state in the model and the TRAILBLAZER-ALZ 2 trial



Abbreviations: AD: Alzheimer's Disease; BSC: best supportive care; TB2: TRAILBLAZER-ALZ 2.

Conclusion

Although broadly aligned, the differences observed in predicted state distribution of the BSC cohort (MCI / Mild / Moderate / Severe), over time, between the model and the TB2 trial, are reflective of differences between the NACC population and the trial population. The NACC population appears to progress slightly faster in the mild health state than the trial population, and the transition probabilities in the model are based on the NACC population. Because the NACC population progresses slightly faster than the TB2 population, the model assigns relatively more patients to the moderate and severe health states over the first 18 months than is seen in the TB2 trial, and relatively fewer patients to the mild health state.

We consider the NACC data set to be more reflective of a real-world context than the patients enrolled in the clinical trial. Real-world evidence is typically preferred over trial data to inform chronic disease progression, as it has a larger sample size and a longer follow up time. In the economic model, the clinical trial data have been used to establish the relative treatment effect as it is a randomised placebo-controlled phase III trial, while the NACC data set has been used

to represent progression on best supportive care in the real-world population expected to benefit from the medicine. Based on Garcia et al.,[48] Lilly found no evidence of treatment effect modifiers between the clinical trial population and NACC population, and therefore we consider it appropriate to apply the hazard ratio derived from the clinical trial to model the treatment effect.

Section C: Textual clarification and additional points

C1. There is an asterisk in CS Appendix B.1.1.1, Table 1, within the 'Inclusion criteria' column of the 'Population' row, but no associated footnote. Please supply the footnote or clarify if the asterisk is redundant.

Lilly can confirm that the asterisk is redundant and was added in error.

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NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Donanemab for treating mild cognitive impairment or mild dementia caused by Alzheimer's disease [ID6222]

Patient Organisation Submission

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type. [Please note that declarations of interests relevant to this topic are compulsory].

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you

1.Your name	[redacted]
2. Name of organisation	Alzheimer's Research UK
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	Alzheimer's Research UK is the UK's leading dementia and Alzheimer's disease research charity. We are dedicated to understanding the causes of dementia and developing ways to prevent, treat and ultimately, cure, all forms of the condition. To do this, we are investing in the best research and working with government, parliamentarians, clinicians, industry and people impacted by dementia. We receive 96% of our income from donations from the public.
4b. Has the organisation received any funding from the company bringing the treatment to NICE for evaluation or any of the comparator treatment companies in the last 12 months? [Relevant companies are listed in the appraisal stakeholder list.] **If so, please state the name of the company, amount, and purpose of funding.**	Alzheimer's Research UK has received funding from the company in the last 12 months as part of the Dementia Consortium project. The Dementia Consortium brings together experts in target biology from academia and drug discovery experts from industry. The project provides funding and in-kind support for research projects typically 2 to 3 years in duration. Alzheimer's Research UK and the Dementia Consortium Industry partners, which includes Eli Lilly, share the cost and risk of early-stage dementia drug discovery. **VAPB: ER-mitochondria signalling as a new target for Dementia (VAPB-PTPIP51 tethering)** • Status: Ongoing • Funding: Eli Lilly provided £24,355.58, October 2023 **Attending Eli Lilly Global Team Advisory board** • Direct travel and subsistence costs reimbursed £57.35
4c. Do you have any direct or indirect links	No

with, or funding from, the tobacco industry?	
5. How did you gather information about the experiences of patients and carers to include in your submission?	In April 2021, we commissioned research into public opinions (including people with MCI and AD) around new treatments, and the challenges they may face in reaching those who could benefit from them. This research involved people with lived experience of mild cognitive impairment and early Alzheimer's, and the findings helped us with developing this submission. In 2021 Age UK Trafford also kindly allowed us to speak with their support group for those with mild cognitive impairment in preparation for Aducanumab submission [ID3763] and some findings are used in this submission. In 2023, we spoke to one lecanemab trial participant and three carers/partners of lecanemab trial participants found through discussions with clinicians at NHS trial sites for [ID4043] appraisal. In January 2024 we spoke to a donanemab trial participant who got involved to the trial via a Re:Cognition Health site. For transparency, we have distinctly indicated the sources of evidence in questions 9 and 10. We also asked volunteers with lived experience of Alzheimer's disease who are members of our Policy Insight and Experience Panel[i] to review relevant parts of our draft. Over the years, we have published a number of reports exploring how to progressively reform and build dementia diagnostics capability, public attitudes towards dementia,[ii] and analysis of system readiness to adopt new innovations.

Living with the condition

6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	Alzheimer's disease is a progressive disease which causes dementia and ultimately death. Every person's experience of mild cognitive impairment (MCI) due to Alzheimer's disease and early-stage Alzheimer's disease is different and unique. However, many people find everyday activities like going to the shops, remembering appointments, and managing bills and letters difficult. *"In work… when I first realised there was a problem, was when I suddenly couldn't remember to do the things (I had) done every day for 15 years." (person living with MCI)* New environments can also present challenges, including interacting with new people who may not be familiar with their condition. People progressing into moderate and severe stages of Alzheimer's disease will need more support with everyday tasks and an increasing amount of care as time goes on. The severest stages of dementia can lead to people no longer being able to converse, recognise loved ones or maintain self-care – often requiring significant residential care. Near the end of life, the person may be in bed most or all of the time due to the severity of their symptoms.

	"You go from being a very confident person, working, to someone who you don't recognise in yourself…" (person with MCI) Mild cognitive impairment and early stages Alzheimer's also have a distinct effect on loved ones, many of whom take up a role as informal carer. Care partners face significant burden in caring for individuals with Alzheimer's disease, and the severity of burden increases substantially as the disease progresses to more advanced stages.[iii] In addition to physical symptoms, carers manage difficult changes in their loved ones' behaviour and personality, including aggression in some cases. *"She'll fight me, you can see the little marks there where she's trying to pinch me all the time, and she'll try and bite you, and slap you and all kind of stuff."[iv] (carer for a person with Alzheimer's disease)* Informal carers are at a significant risk of depression, anxiety, and social isolation.[v] In addition to reduced work opportunities and income, there are direct financial costs to providing care including but not limited to higher energy bills and higher transport costs. *"They asked me to be a team leader at work. As soon as they asked me I was like, 'Well, my mum.' I could have gone for it, but because of mum, pretty much didn't." (carer for a person with Alzheimer's disease)* 48% of carers also have a long-standing illness or disability themselves, indicating both the mental and physical toll of the condition.[vi] Caregiving is often a shared responsibility among multiple family members, impacting not only the individual and their immediate partner but also other relatives. This collective burden frequently leads family members to forgo personal activities. *"There's a lot of mental stress there because you're thinking, frightened to sleep, what if he gets up and wanders out of the door during the night? I'm worn down… I lie at night and I go, 'Well have I done this? Have I done that?' Then I'm starting to question myself."[vii] (carer for a person with Alzheimer's disease)* With mild cognitive impairment, an important and frequently reported challenge to getting a diagnosis was a general lack of understanding about MCI by family members and friends.

Current treatment of the condition in the NHS

7. What do patients or carers think of current	Treatments available to people in the UK with MCI and early Alzheimer's disease today are symptomatic treatments, such as Cholinesterase inhibitors.[viii] These treatments can stabilise or slightly improve a person's symptoms, often their thinking and memory problems, and can help them to maintain their ability to carry out day-to-day tasks independently. This can

treatments and care available on the NHS?	make a big difference to someone's quality of life, but these drugs can have side effects, they do not work for everybody, and the effect is time-limited as the disease continues to progress. Half of general public think that current dementia treatments are not effective, just 19% consider them to be effective and a significant proportion (29%) are unsure either way.[ix] Members of our Policy Insight and Experience Panel noted that health professionals often do not consistently monitor the intake of symptomatic drugs. This leaves carers uncertain about symptomatic treatments' effectiveness in helping patients. Symptomatic drugs also do not continue to work effectively when someone's dementia becomes more severe. As these treatments can't slow or stop the underlying damage getting from worse in the brain, their beneficial effects usually only last for 1-2 years. *"…the consultant told me that once the memantine [sic] stopped working it would be like falling of [sic] a cliff regarding his symptoms and there was nothing then that would help.....they were right."* (caregiver)[x] There has not been a new treatment for Alzheimer's disease for nearly 20 years. Knowledge of this prompts both shock and outrage both among those with lived experience of the condition, and the wider public.[xi] *"17 years…that's shocking, that's outrageous…I had no idea. I'm shocked and disgusted."* (Alzheimer's Research UK supporter, quote from 2021)
8. Is there an unmet need for patients with this condition?	Dementia is one of the leading causes of death in the United Kingdom, with over 944,000 people estimated to be currently living with the condition in the UK. Alzheimer's disease is the most common cause of dementia (50–75% of cases[xii]). Age is the biggest risk factor for dementia although 7.5% of all people with dementia have young onset dementia. With an ageing population, current projections anticipate that prevalence of dementia could rise to 1.1 million by 2030.[xiii] There are currently no treatments available in the UK that have an impact on disease progression for those with mild cognitive impairment due to Alzheimer's disease and Alzheimer's disease. There are no licensed treatments for amyloid positive MCI, and limited treatment options for mild, moderate and severe Alzheimer's disease. Previously approved AChE inhibitor treatments have provided 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. Through both our insight building work with those with a lived experience of dementia, as well as with a wider public audience, there is a sense that Alzheimer's disease feels "underserved" by the NHS. *"(a potential treatment)… for me that is like the first potential treatment of cancer, you know it's a start. For such a cruel disease to have some hope…"* (patient with MCI)

Advantages of the technology

9. What do patients or carers think are the advantages of the technology?	If people could access new disease-modifying treatments, then the typical pattern of decline experienced by those living with Alzheimer's disease could be changed. This means it would improve a person's ability to function independently for longer, may stop symptoms from getting worse, and provide the opportunity for individuals to engage in meaningful activities, as well as plan for the remaining time in the best way, enhancing their overall quality of life. *"If you had another six months with more clarity, more purpose for them, more purpose for you, how amazing would that be?" (carer)* Maintaining individual independence over an extended period could also have positive implications for those supporting loved ones, such as allowing carers to sustain employment and improving the well-being of families affected by dementia, resulting in overall benefits to the economy. Alzheimer's Research UK commissioned research to understand the outcomes from new treatments that matter most to people. Among all demographics, family connections, driving, socialising, reading, and friendships rank as the highest priority outcomes for new treatments.[xiv] These are not included in the Clinical Dementia Rating Scale (CDR) which clinicians and researchers employ to evaluate the severity of dementia. Through our engagement with those who have lived experience of MCI, we know there is support for approval of a drug that can provide *some* level of clinical benefit. People understand that a treatment such as donanemab will come at some cost to the NHS, however they also recognise how a drug could have the potential to generate savings in care and informal care if it slows down disease progression. *"(a treatment) that means people don't need extra help, must be a good thing for the NHS…" (patient with MCI)* We have been able to find one person who has had the treatment via a private site. The participant in the trial remains unaware of whether he received a placebo or the actual drug, but he has been receiving donanemab since March 2023 as part of the trial extension, set to finish in September 2024. The patient holds a positive view of the drug, whereas his wife, who is a former nurse, is a bit more sceptical. *"I do not appear to be slipping down that terrifying slope into dementia. … That's my experience of donanemab. I'm very positive about it. … To most people I'm actually feeling perfectly okay. I can have conversations but sometimes there will be this blank bit, and it basically means I'm losing my plot. I don't quite remember what it is that I'm supposed to be doing. This continues … It's [donanemab] keeping me at the same level as I was 10-15 years ago*

	which is as I understand it as much as we can expect from any of these drugs. … She [wife] has seen a deterioration in me, whereas I don't. I think I'm on the same level", - Patient 1, who participated in the donanemab clinical trial. In a separate conversation with Patient 1's wife, she noted that he "never gives up". She mentioned that she wouldn't mind if he continued taking the drug, acknowledging that the decline is still present but happening at a slow pace.

Disadvantages of the technology

10. What do patients or carers think are the disadvantages of the technology?	While lecanemab and donanemab target amyloid-beta plaques at different stages as they build up in the brain, both drugs are monoclonal antibodies with similar delivery mechanisms, monitoring requirements and side effects. The commonalities justified the inclusion of some insights obtained from lecanemab trial participants to the answers below. Trial participants (and their carers) reported several challenges and disadvantages associated with the new disease-modifying drugs. These issues ranged from difficulties during the infusion process, concerns about lack of medical equipment and staff expertise, to their experiences with MRI and PET scans. Additionally, one patient initially on a placebo, who got the lecanemab via extension label, experienced small brain bleeds, leading to concerns about the medication's safety and effectiveness. **Infusion Process Experiences** The drugs are administered at an infusion suite. Patients and carers faced challenges during the infusion process, including occasional discomfort during the insertion of a cannula and the need for multiple attempts to place the cannula into the patient's vein. Some of the medical staff who were not regularly carrying out the procedure (mental health nurses and psychiatrists) sometimes experienced difficulties in locating veins, further complicating the infusion process. *"[Patient 3] remembers that there were times when inserting the cannula was quite painful. … After one particular occasion he said to me that he felt a little bit like one of those Red Cross dummies because there were problems getting the cannula in. And one doctor said to the other: 'would you have a go?'*", - carer for Patient 3, who participated in the lecanemab clinical trial. Concerns were raised about the reliability of medical equipment and the expertise of the medical staff, with issues related to infusion pumps, equipment settings, and the handling of infusion kits. The initial NHS trial site visits were notably time-consuming, often taking up an entire day and involving multiple hours for infusions, observation, and blood tests. However, over time, the visits became shorter for some participants. We know that some patients will have had their trial through neurology teams which might have been more used to the set up. We would expect with greater experience of the procedure many of these issues would be resolved.

MRI and PET Experiences

Some individuals found MRI scans to be efficient and quick, with minimal waiting time. One carer noted that MRI scans conducted by the university MRI team offered a quieter and more civilised environment compared to a general hospital. However, for some, MRI scans were challenging due to the requirement to stay still and with minimal stimulation.

> *"I'm getting used to it, but I have a predisposed negative attitude to being trapped inside anything. It usually takes 20-25 minutes under the scan. I have asked them every time 'please give me some timings' because just lying there… after ten minutes it's okay, [after] twenty minutes my brain starting 'come on, you got to get out of here'. You can't move your head either way or it has to be redone",* - Patient 1, who participated in the donanemab clinical trial.

> "*There were a lot of MRIs and PET scans which [Patient 2] found very difficult. In the end that was why he had to come off the drug because he couldn't stay still in the MRI. He was really struggling. He couldn't understand that he had to stay absolutely still. … He was just twitchy*", - carer for Patient 2, who participated in the lecanemab clinical trial.

Participants in clinical trials found PET scans challenging due to the need for staying still, being isolated, and need for precise timings.

> *"PET scan is tricky on timings because they have to bring… I don't know what the chemical is [radioactive tracer] but it's one which has to be brought from the Midlands at the certain time of day. … And they [chemicals, scans] have to be prepared for some time. You have to sit there for about fifty odd minutes after some stuff has been injected into your arm with nobody coming in because of the uranium aspect of it. No nurses, nothing like that. At the end of fifty minutes, you head towards PET",* - Patient 1, who participated in the donanemab clinical trial.

> "*He found it very hard as well because you are supposed to lay still with virtually no stimulation. I was not even encouraged to be in the room to talk to him and sort of keep him quiet. I was allowed in a couple of times because they started to realise he was struggling. But he found PET scans really hard-going because of the amount of time he was just left on his own on the trolley after [the tracer] has been administered. … he did say that they were a bit of a bind to do*", - carer for Patient 2, who participated in the lecanemab clinical trial.

Amyloid Related Imaging Abnormalities (ARIA)

In the phase 3 trials of donanemab, the reported rates of ARIA-E were 24.0% and of ARIA-H 31.4% [xv]. The donanemab trial participant we spoke to has not experienced ARIA, but the data shows that ARIA is a concern and should be closely monitored.

	Travel While most participants we interviewed indicated that travel for the trial procedures, including driving up to three hours a day, was not a significant problem, it's important to consider that in the trial setting, certain expenses were covered by the company. In the real world, individuals and their families might need to travel long distances to access the required facilities, which could result in additional costs that need to be considered. This is particularly relevant in parts of the country where MRI and PET infrastructure may be limited or less accessible. Additionally, it is possible that initially, the drug could be deployed at a limited number of centres, necessitating longer travel times. **Tolerance of risk** Alzheimer's Research UK commissioned research to understand attitudes to risk for hypothetical treatments which would delay the progression of Alzheimer's Disease.[xvi] Including people who reported living with memory problems, this found that: • More than half of the respondents were willing to accept what would be considered very high risks from a regulatory perspective – this might be due to the irreversible consequences of the progression of dementia, which will lead to less independence, poorer quality of life and early death: o 1 in 2 people were willing to accept up to a 10% risk of severe side-effects. o 1 in 4 people were willing to accept a greater than 50% risk of moderate side-effects.

Patient population

11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	• Alzheimer's Research UK acknowledges that the scope now includes 'ApoE4 carrier status' as a subgroup. The APOE gene is the most significant genetic risk factor for Alzheimer's disease[xvii], with APOE carriers facing a higher risk of ARIA[xviiixix]. This highlights the vital necessity for testing for APOE genes which currently is not routinely provided by the NHS. At present, there is a lack of evaluations conducted on the costs and scale of implementing such testing within the NHS. Clinicians will need to engage in conversations about APOE status with their patients — a practice not currently integrated into routine clinical discussions. • Given challenges around MRI and pacemakers[xx] this will be a specific issue which will need further evaluation. This issue was reflected in the conversations we had with trial participants. • The early-onset population could experience greater benefits from the treatment due to amplified impact on families' costs and fewer associated health complications. While we recognise that age is a protected characteristic, this viewpoint was brought forward by individuals with lived experience.

Equality

12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	• 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.[xxi] It is unlikely that services across the UK will be uniformly ready to treat and manage patients on donanemab if and when it becomes available. Moreover, if MHRA will require confirmed tau pathology, it's important to note that, based on our current understanding, there are no commercially available tau PET ligand tracers for use in the UK. • Much of current molecular biomarker diagnostic access is located within predominantly neurology led research centres, with access through research studies rather than NHS service delivery. This division in access by clinical specialty could add to geographical inequity to diagnostics. • The studied populations in the donanemab trial were predominantly White (91.5%), potentially limiting the generalisability of the findings to other groups due to a lack of racial and ethnic diversity[xxii]. • People from lower socio-economic backgrounds, black people and women are both more likely to develop dementia [xxiii] [xxiv] [xxv], less likely to get a diagnosis [xxvi] and as a result less likely to come forward to seek treatment. Discussion of equality issues should also include the consideration that over 60% of dementia carers are women.[xxvii] • The lifetime risk of Alzheimer's disease in people with Down's syndrome is more than 90%,[xxviii] and it is the leading cause of death in this population.[xxix] 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.[xxx] Additional consideration may be needed to prescribe this medication to people with Down's syndrome.

Other issues

13. Are there any other issues that you would like the committee to consider?	Need for a joint conversation between MHRA, NICE, NHS ▪ We propose that MHRA, NICE and NHS work together to find solutions for the possible challenges linked to donanemab. The collaborative effort could generate innovative solutions or consider adaptable approaches like a managed access scheme through the Innovative Medicines Fund (IMF) which should include robust data collection. A data collection agreement should be developed jointly with patient groups and reflect the safety profile and long-term outcomes of the treatment, including but not limited to the expected duration of treatment and stopping criteria. ▪ The full benefits of donanemab may become more evident in the long-term, particularly as greater care costs are associated with moderate to severe stages of dementia and will prove challenging to evaluate as the Phase III trial only covered eighteen months in a carefully curated population. Given the potential benefits and high unmet need

	it is important to acknowledge uncertainty not as a negative aspect but as a gap necessitating attention. Flexibility in cost-effectiveness assessment should be considered given the inherent nature of this data uncertainty. Opportunity and challenges for infrastructure and system readiness **Molecular biomarkers and other diagnostics requirements** ▪ Amyloid PET and CSF sample via lumbar puncture are recommended as a standard of care in NICE guidelines.[xxxi] Alzheimer's Research UK would like to challenge the point raised by NHS England in the consultation on draft scope on capacity and costs associated with diagnosis being considered in the appraisal. Our view is that PET and CSF are not new to the system, as they are used more widely in other disease areas as well as for diagnosis of Alzheimer's. The historic underinvestment in diagnostic infrastructure for Alzheimer's disease and lack of commissioned NHS services for PET and CSF testing reflects a system challenge. There are also other disease-modifying treatments in the pipeline, and it would not be equitable to include the costs of diagnostics for one drug's HTA. Therefore, in the case of disease modifying treatments, diagnostic costs should be considered outside the scope of a Single Technology Appraisal. ▪ Current access to amyloid PET and CSF in the diagnosis of Alzheimer's disease is limited within NHS services and scaling up one or both will be challenging. Very few scans or lumbar punctures are currently commissioned through NHS services – in the 2019 Memory Audit Clinic only 2% of patients were referred for such specialist investigations.[xxxii] There is limited data on the use of PET scanners in dementia diagnoses, but it is understood that the majority of current capacity is used by oncology services with limited additional capacity for Alzheimer's disease diagnosis.[xxxiii] Similarly, CSF has limited current use in the diagnosis of Alzheimer's disease.[xxxiv] ▪ Multiple MRI scans will likely be required for monitoring of Amyloid Related Imaging Abnormalities (ARIA). In the UK, existing limited MRI capacity is already a bottleneck in the dementia diagnostic pathway. Scan wait times, (e.g., average of 5 weeks for MRIs) were already acknowledged prior to the pandemic to be "a key barrier" in meeting the national six-week referral to treatment goal.[xxxv] As such, this added requirement to frequently monitor for adverse events like ARIA using MRIs, means that – as with molecular diagnostics – capacity will likely need to be scaled up. Wider societal benefit ▪ NICE should use existing flexibilities to include relevant wider societal benefit in the donanemab evaluation. NICE has previously considered wider impacts in specific evaluations such as nalmafene[xxxvi] and should do so in this case. NICE should clearly indicate how wider effects have been factored into the evaluation, ensuring reflection in relevant documents and discussions during committee meeting. ▪ Given that donanemab might offer substantial benefits extending beyond the NHS and Personal Social Services (PSS), we recommend that NICE highlights these advantages to relevant governmental bodies, such as the Department of Health and Social Care, to ensure a broader recognition of the potential societal impact of this treatment.

	▪ Approximately 55% of people living with dementia are in the mild stages, with 32% in the moderate stages and 12% in the severe stages[xxxvii]. 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. ▪ More than a quarter of people with dementia are in care, and this has an annual cost to the economy of £10.8 billion[xxxviii]. 60% of people receiving home-care services are living with dementia[xxxix]. In England and Wales, the number of people living with dementia who need palliative care will almost quadruple by 2040[xl]. <u>Carer quality of life</u> ▪ NICE has included health related quality of life (HRQoL) as an outcome to the scope for this appraisal, which includes carer quality of life (QoL). We advocate for a clear indication from NICE on how carer QoL has been factored into the evaluation, ensuring reflection in relevant documents and discussions during committee meeting. ▪ 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. There are an estimated 700,000 informal carers caring for those living with dementia in the UK. 1.3 billion hours are spent on unpaid informal care for dementia, and recent economic modelling indicates that this given a formal cost would be seen at £8.8 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[xli].

Key messages

14. In up to 5 bullet points, please summarise the key messages of your submission.	• Donanemab represents a new class of treatment for MCI due to Alzheimer's disease and early Alzheimer's disease which could alter the natural course of the condition. • Approval of donanemab has the potential to be the catalyst for delivering a large-scale, much-needed step change in the care and diagnosis of those with Alzheimer's disease and mild cognitive impairment due to Alzheimer's disease. • MHRA, NICE and the NHS must work together to find solutions to the possible challenges linked to the approval and use of donanemab in clinical practice. We recognise that the drug poses uncertainty regarding costs and benefits but given the huge unmet need we believe that adaptable solutions like a managed access scheme which includes data collection should be urgently considered. • Alzheimer's disease has a severe effect on the physical and mental health of carers, and NICE should be clear on how the effect of the treatment on carer quality of life has been reflected in their incremental cost-effectiveness ratio (ICER) consideration.

	• Wider societal value from a dementia treatment 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. NICE should be clear on how the current methodological flexibilities have been used to consider it.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

Please select YES if you would like to receive information about other NICE topics - YES or NO

For more information about how we process your personal data please see our privacy notice.

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[xix] Rising Leqembi Prescriptions Are Straining Clinic Capacity | ALZFORUM
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NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Donanemab for treating mild cognitive impairment or mild dementia caused by Alzheimer's disease [ID6222]

Patient Organisation Submission

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type. [Please note that declarations of interests relevant to this topic are compulsory].

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you

1.Your name	[redacted]
2. Name of organisation	Alzheimer's Society
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	Alzheimer's Society is the UK's leading dementia charity. We provide information and support, improve care, fund research, and create lasting change for people living with dementia in England, Wales, and Northern Ireland.
4b. Has the organisation received any funding from the company bringing the treatment to NICE for evaluation or any of the comparator treatment companies in the last 12 months? [Relevant companies are listed in the appraisal stakeholder list.] **If so, please state the name of the company, amount, and purpose of funding.**	Alzheimer's Society has not received funding from the manufacturer of donanemab or comparator products in the last 12 months.
4c. Do you have any direct or indirect links	No

with, or funding from, the tobacco industry?	

5. How did you gather information about the experiences of patients and carers to include in your submission?	• We sought to obtain evidence from people living with dementia on their views on the advantages and disadvantages of donanemab, taking the same approach as with our response to the NICE appraisal of lecanemab - conducting a focus group and distributing a survey. Levels of engagement were lower, with only four people attending the focus group and only 30 responses to the survey (which was sent to 320 people). We believe that proximity to Christmas may have affected engagement levels.
	• To address the small sample size, we will present only the key findings from this evidence-gathering, and we will be clear about sample sizes throughout the submission.
	• We will supplement this with evidence we obtained for the lecanemab appraisal, where we believe responses have relevance to disease modifying treatments (DMTs) in general. However, we also recognise that there are differences between the two drugs, in their benefits and in their side effect profile. For example, a larger proportion of participants taking donanemab were found to have amyloid-related imaging abnormalities (ARIA) (36.8%[1]) than in the lecanemab trial (21.5%[2]). ARIA are some of the side effects of greatest concern as serious cases can potentially be fatal. ARIA relates to changes in the brain found in MRI scans that are related to the use of amyloid-clearing drugs, either in the form of swelling or bleeding in the brain, although the majority of people in the donanemab trial with ARIA had no symptoms. In the main donanemab trial, three deaths were considered to be related to treatment with donanemab. This is compared to no treatment-related deaths in the main lecanemab trial; however, three have been reported in the extension phase[3]. These differences in side effects may limit the extent to which responses related to lecanemab are applicable to both drugs but our response is clear when citing evidence obtained for lecanemab, so that this can be taken into account.
	• For our lecanemab appraisal evidence gathering, we:
	  ○ Conducted an online focus group on 3 November attended by 6 people living with Alzheimer's disease and 7 unpaid carers for people with Alzheimer's disease.
	  ○ Sent a survey, via email, to our campaigners to find out their views on the advantages and disadvantages of lecanemab. The email included a summary of the lecanemab trial results

[1] https://jamanetwork.com/journals/jama/fullarticle/2807533
[2] https://www.nejm.org/doi/full/10.1056/NEJMoa2212948
[3] https://www.science.org/content/article/scientists-tie-third-clinical-trial-death-experimental-alzheimer-s-drug

	and a link to our blog for further information. Our campaigners, many of whom are directly affected by dementia, are people who have signed up to hear about and take action to support our campaigning work. We analysed the responses from 238 people who identified as being personally affected by Alzheimer's disease. • For the questions related to experiences of living with dementia, we reviewed discussion threads on Alzheimer's Society's online community, the Dementia Support Forum, specifically reviewing the most recent 200 threads in the categories 'I have dementia' and 'I care for a person with dementia' to identify key relevant themes. It wasn't possible to identify responses specific to Alzheimer's disease as opposed to other types of dementia from this source. • We have drawn on our existing knowledge of dementia, which is detailed on our web pages including these pages in particular: ○ https://www.alzheimers.org.uk/about-dementia/symptoms-and-diagnosis/how-dementia-progresses/later-stages-dementia ○ https://www.alzheimers.org.uk/about-dementia/types-dementia/alzheimers-disease-symptoms#content-start ○ https://www.alzheimers.org.uk/get-support/staying-independent/driving-dementia • We have included evidence from a survey conducted in 2021/22 for Alzheimer's Society's 'Left to cope alone' report, which was completed by 914 people living with dementia. It wasn't possible to identify responses specific to Alzheimer's disease as opposed to other types of dementia from this source. • We have also cited research studies and other literature (references are included). • We tried to find people who participated in the donanemab trial via our networks but were unable to find anyone who had participated in the trial fully.

Living with the condition

6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	Experiences of people living with Alzheimer's disease can vary significantly. As it is a progressive disease, it is inevitable that symptoms worsen over time, meaning people's experiences differ in the earlier and later stages of the condition. At Alzheimer's Society, we often hear people say that 'when you've met one person with Alzheimer's disease, you've met one person with Alzheimer's disease.' This statement was directly quoted in one of our focus groups and reflects the risk of making general assumptions on what it's like to live with the disease. The most common symptoms of Alzheimer's disease in the early to middle stages of disease progression are memory loss; difficulties with daily tasks due to struggling with concentrating and planning; changes in mood, becoming agitated and losing interest in things; and problems with language and following conversations. Alzheimer's disease can also have a significant impact on individual and carer mental health, with many people developing anxiety or depression. A survey found that 61% of people affected by dementia are currently in need of mental health support[4]. Some people with dementia using the Dementia Support Forum report worrying about being a burden to their family and other loved ones and feeling afraid for the future [online forum]. Alzheimer's disease also progressively limits people's ability to carry out daily activities and hobbies outside of the house. By the middle stages of Alzheimer's disease, most people will need to stop driving and using public transport, though in some cases this may happen sooner. In turn this then limits a person's independence and ability to undertake daily activities like socialising, shopping and maintaining hobbies and interests that are crucial to overall quality of life. 'Sometimes I sit and try to think about certain things and the one thing that always pops up and makes me so incredibly sad is trying to remember the last time I went out on my own, anywhere. For the last ten years I have been told I have lost my road sense' [online forum]. 'We used to travel a lot, especially RV trips in the US. I kind of think I need to pull myself together and do something before it's too late for me' [online forum]. Some people of working age with Alzheimer's disease may continue working for a time with the right support and adjustments from their employer. However, most people will need to give up work due to the impact of their symptoms as the condition progresses.

	'I was with my brother when he was told he was being medically retired by his Company at just 58 years old. He was a senior archaeologist, the only job he'd ever had' [online forum]. In the later stages of Alzheimer's disease, many people will struggle with their memory of recent events and may think they are at an earlier period of their life. They may stop recognising familiar places, objects and people, including loved ones. Speech may be reduced to only a few words or lost altogether. They may also understand fewer words, but they may still be able to understand and use non-verbal communication. Factors such as these contribute to dementia overall sometimes being referred to as 'the long goodbye.' Depression and apathy can become more common in the later stages, and people can develop delusions and hallucinations. People may often feel scared or confused. Alzheimer's disease can lead people to experience increased agitation in the late afternoon and early evening, known as sundowning. They will experience increasing frailty and more drastic physical symptoms such as walking more slowly, issues with eating and swallowing, and incontinence, and are at greater risk of falls and serious infection[5]. Over time, people living with Alzheimer's disease will struggle with tasks of daily living and personal care, such as eating, washing and dressing, and will need increasing levels of support. This often results in unpaid carers providing many hours of care, taking its toll on their own health and wellbeing – as will be discussed more in the next question. Many people with Alzheimer's disease will at some stage need to draw on support from social care. It is estimated that 70% of people living in care homes have dementia[6], and that 60% of people who draw on support from homecare are people with dementia[7]. 'Did anyone ever tell you that because the person can't go out at night because of sundowning your friend's [sic] list would shrink, the invites would stop, even the ones for during the day because dementia has raised its ugly head?' [online forum]. 'Sometimes when I walk into the room and see my Angels [sic] face, drawn with worry and trying to figure out the best way forward for the future, what am I supposed to say? Do I say I am sorry? Do I pretend I haven't seen her? Do I lie to her and say everything will be ok when quite clearly, it's not going to be? Nobody told me this would happen!' [online forum].

[4] https://www.alzheimers.org.uk/sites/default/files/2022-07/left-to-cope-alone-after-diagnosis-report.pdf
[5] https://www.alzheimers.org.uk/about-dementia/symptoms-and-diagnosis/how-dementia-progresses/changes-in-behaviour-later-stages
[6] The cost of dementia in England, Wittenberg et al 2018
[7] Dementia and homecare: driving quality and innovation, UKHCA, 2015

	As part of an APPG on Dementia report, Alzheimer's Society conducted a survey of nearly 2,000 people living with dementia who draw on social care in which we asked respondents to identify key dementia-specific needs of which the social care workforce should have knowledge and understanding. Common answers included people struggling with communication and expressing themselves, how staff could respond appropriately to behaviour that challenges, and the benefits of meaningful cognitive stimulation activities for an individual's health and wellbeing[8]. The survey also highlighted the importance of support that goes beyond personal care. Many people living with and affected by dementia expressed that they wanted to be supported to do the things that matter most to them and that offer a sense of meaning and purpose. This could be continuing a favourite hobby or getting out to see friends. It is important to recognise that ultimately, dementia reduces life expectancy and is the leading cause of death in the UK[9]. Dementia also has a significant impact on the health and social care system – in the UK £16.9billion is spent on social care for people living with dementia every year, and £5billion is spent on NHS care[10]. As there is little specific support available for carers of people living with dementia, Alzheimer's disease can also lead to a decline in carer health and wellbeing. During our focus group we heard about people giving up work and struggling with sleep due to their caring role. Being unable to take a break was also a common theme. Carers' mental, physical and emotional wellbeing often deteriorates as a direct result of caring[11], with people regularly reaching breaking point, stressed and unable to cope with the demands of caring. 39% of carers for people living with dementia provide over 100 hours of care a week[12].

[8] https://www.alzheimers.org.uk/sites/default/files/2022-09/APPG%20on%20Dementia%20Workforce%20Matters%20Report%202022.pdf
[9] https://www.alzheimers.org.uk/about-us/dementia-UK-leading-cause-of-death
[10] https://www.alzheimers.org.uk/sites/default/files/2019-11/cpec_report_november_2019.pdf
[11] https://www.alzheimers.org.uk/sites/default/files/2022-07/left-to-cope-alone-after-diagnosis-report.pdf
[12] Personal Social Services Survey of Adult Carers in England, 2023

	'I found it very hard to come to terms with the fact that I was now a full-time carer. It really is a 24/7 job. I feel stressed every waking minute.' [Left to cope alone report] 'I'm exhausted, worried, angry, frustrated and nobody seems too interested. In the middle of the night, struggling to get my wife, in pain, partially incontinent, out of bed and to the toilet I feel desperate, utterly shattered and alone.' [Left to cope alone report] 'There is no area of my life that hasn't been affected'. [Left to cope alone report] Many carers reduce their working hours or give up working completely due to their caring responsibilities. Over 147,000 working age carers supporting a person with dementia have had to reduce work commitments or are having difficulties balancing work and caring, and a total of 112,540 working age carers are no longer in paid employment due to their caring responsibilities[13].

[13] The economic cost of dementia to English businesses, CEBR, 2019

Current treatment of the condition in the NHS

7. What do patients or carers think of current treatments and care available on the NHS?	The focus group (carried out to inform our response to the lecanemab appraisal) found that people are eager to access any treatment or care that will help to slow progression and/or manage the disease. Most of all, people want treatments that will give them more time to live a 'normal' life and to spend time with loved ones. Drugs that are currently available (memantine, donepezil, galantamine, and rivastigmine) are only able to help with symptoms of memory and thinking problems temporarily; they do not slow progression of the disease. Views on current symptomatic drug treatments are very mixed due to the wide range of different experiences people have of taking them. Based on the focus group and our online forum, while some people reported benefits of current symptomatic drugs including reduced agitation, improved ability to perform some daily tasks, remain focussed, and have confidence, a reduction in nightmares and confusion, and reduced mood swings, others reported significant side effects. These included increased agitation, dizziness, nightmares, and more. In some cases, treatments appeared not to offer any benefits or left people unsure of whether they were helpful or not; and many were only found to be beneficial for a short period of time. Concerns were also raised about people not being monitored while taking treatment, and having to persevere to get a follow-up and review. Non-pharmaceutical forms of support for people with Alzheimer's disease include: dementia advisers and dementia support workers who offer one-to-one support, practical advice and information; social groups (such as activity groups, dementia cafes, peer support groups, and singing groups); respite care; online communities; practical aids, adaptations and technology; and therapy and structured activities (including cognitive stimulation therapy and reminiscence work)[14][15]. For people with moderate to advanced dementia, many people will need support from social care, primarily through homecare or residential care. However, people often struggle to access many of the types of support listed here, as will be covered in the next question.

[14] https://www.alzheimers.org.uk/about-dementia/types-dementia/treatment-support-alzheimers-disease#content-start
[15] https://www.alzheimers.org.uk/get-support/your-local-dementia-support-services

8. Is there an unmet need for patients with this condition?	More than a third of people with dementia in England[16] and Northern Ireland[17] and half of people with dementia in Wales don't have a diagnosis[18.] This is despite 91% of people saying that they benefitted from receiving one[19.] A diagnosis is vital to help people understand the reasons for their symptoms and to enable them to plan for the future. It also unlocks access to care, symptomatic treatments, information, advice and opportunities to participate in research. The lack of timely and accurate diagnoses is the single biggest challenge we currently face in the dementia space. It is vital that Government and the NHS work together to meet the national diagnosis rate target in England via a clear plan with funding and a timetable for delivery attached. There must also be a drive towards setting a more ambitious diagnosis rate for the future. Many people with dementia *with a diagnosis* also struggle to access support. A survey found that three in five (61%) people living with dementia did not feel supported by the health and social care system to cope with their or their loved one's diagnosis and to manage the condition[20]. In our focus group, people discussed their experiences of a lack of available support and the unfairness of this compared to the support that they expected they would have received if they had developed another condition. People described feeling abandoned and overwhelmingly wished that they had more support – a sentiment that is also covered on our online forum. A survey conducted for our *Left to cope alone* report demonstrated a number of challenges in accessing support. Despite the importance of person-centred support, focusing on the needs of the individual and taking into account their life history, needs and preferences, 48% of people reported that they currently lack person-centred support. People affected by dementia value peer support and social contact[21], yet 21% of people said they currently lack peer support and 31% said they lack support to help maintain their social life. Support to help preserve cognitive skills is vital for people with dementia, yet 47% of people said that they lack support that helps them use these skills. Despite the importance of Cognitive Stimulation Therapy (CST) being recognised in the NICE dementia guideline[22,] a national audit of memory services found that 25% of services did not provide CST or were unable to refer to another service for the therapy[23]. Care plans and reviews are vital to set out the care and support people need to manage their condition and ensure that as dementia progresses, adaptations are made to suit changing needs. Despite this, 40% of people with a diagnosis of dementia have not received a care plan or a care plan review within the last twelve months[24]. Additionally, a study found that just 29% of people with dementia and 39% of carers said they had a health professional to contact should they need support at any time[25].

	When Alzheimer's disease progresses and needs become more advanced, many people need to draw on social care. However, people are faced with a care system that is costly, difficult to access, and too often not personalised to meet people's needs. Unpaid carers also struggle to access the support they need themselves - in a survey, 68% of people said that they are not receiving carer support[26]. Care is expensive, and many people will need to pay for care themselves without any financial support. In the current funding system, an individual with dementia spends an average of around £100,000 on their care over their lifetime[27]. Care is difficult to access, and it is estimated that there are over 200,000 people with moderate or severe dementia and care needs who are not receiving support from social care (instead, receiving only unpaid care or no care at all)[28]. When people do access care, they often find that it doesn't meet their needs and that care staff don't have the skills and knowledge they need to deliver high-quality dementia care. A survey of nearly 2,000 people living with dementia found only 44% rated care staff's understanding of dementia positively and only 37% said that the care received was personalised[29]. The workforce is also over-stretched, with vacancies at 152,000[30].

[16] https://digital.nhs.uk/data-and-information/publications/statistical/primary-care-dementia-data/october-2023
[17] https://www.health-ni.gov.uk/sites/default/files/publications/health/rdp-ni-2023.pdf
[18] https://www.gov.wales/sites/default/files/publications/2019-04/dementia-action-plan-for-wales.pdf
[19] https://www.alzheimers.org.uk/news/2022-05-16/91-people-affected-dementia-see-clear-benefits-getting-diagnosis
[20] https://www.alzheimers.org.uk/sites/default/files/2022-07/left-to-cope-alone-after-diagnosis-report.pdf
[21] Bamford, C. et al. (2021). Key components of post-diagnostic support for people with dementia and their carers: A qualitative study. PLoS One. 16 (12)
[22] https://www.nice.org.uk/guidance/ng97
[23] Cook, L. Souris, H. & Isaacs, J. (2019). The 2019 national memory service audit. Available: https://www. england.nhs.uk/london/wp-content/uploads/sites/8/2020/04/The-2019-national-memory-service-audit. pdf Last accessed 23/03/2022
[24] https://digital.nhs.uk/data-and-information/publications/statistical/primary-care-dementia-data/october-2023
[25] . Van Horik, J.O. et al. (2022). Limited receipt of support services among people with mild-to-moderate dementia: Findings from the IDEAL cohort. International Journal of Geriatric Psychiatry. 37 (3)
[26] https://www.alzheimers.org.uk/sites/default/files/2022-07/left-to-cope-alone-after-diagnosis-report.pdf
[27] https://www.alzheimers.org.uk/about-us/policy-and-influencing/dementia-true-cost-fixing-care-crisis
[28] https://onlinelibrary.wiley.com/doi/full/10.1002/gps.5113
[29] https://www.alzheimers.org.uk/sites/default/files/2022-09/APPG%20on%20Dementia%20Workforce%20Matters%20Report%202022.pdf
[30] https://www.skillsforcare.org.uk/Adult-Social-Care-Workforce-Data/Workforce-intelligence/publications/national-information/The-state-of-the-adult-social-care-sector-and-workforce-in-England.aspx

Advantages of the technology

9. What do patients or carers think are the advantages of the technology?	Based on our additional evidence gathering on donanemab specifically, the most frequently cited advantages from our survey were slowing progression of the disease and enabling people to have a better quality of life for longer. The below responses are in relation to lecanemab, but we believe they could apply to both treatments. The responses are from people living with Alzheimer's disease who do not have direct experience of either drug. The most frequently cited advantage of treatment, cited by 59% of survey respondents, was slowing the progression of Alzheimer's disease. Improving quality of life came second (cited by 29% of respondents) and was also mentioned in our focus group, along with leading a more 'normal' life for longer. 'Anything' that helps (referring to anything that helps slow the disease) was mentioned in our survey (by 14% of respondents) and in the focus group. When people gave examples of what this means for their lives, more time with loved ones was mentioned (by 10% of survey respondents). Some people also mentioned hope (cited by 10% of survey respondents). 'Any time saved in a person's suffering with dementia is so, so precious. Everyone deserves to continue to live their lives as fully as possible, for as long as possible.' [survey] 'Time to enjoy time together, make the most of time, time to plan, adapt and put support in place.' [survey]

Disadvantages of the technology

10. What do patients or carers think are the disadvantages of the technology?	From the evidence we gathered on donanemab, the most commonly cited disadvantage raised via focus group and survey related to concerns about serious side effects of the drug. Among the small group consulted, some people had very significant concerns about the side effects and the deaths that sadly occurred during the donanemab trial. This was similar to the responses we received in relation to lecanemab where the most common response was in relation to the side effects, cited by 38% of survey respondents and discussed in the focus group. There were mixed comments in relation to the side effects: some people said the side effects were serious (6%), some people specifically stated that they believed the benefits outweighed the side effects (5%), and others observed that most treatments have some side effects (2%). Some people commented that the long-term effects were unknown (2%) [survey]. 10% of survey respondents said they saw no disadvantages. Some people highlighted that a diagnosis was key to enabling access to lecanemab and that diagnosis needs to be improved (4%). In the focus group, one respondent said that a disadvantage was that lecanemab is only effective if received early in disease progression and if someone receives a diagnosis early – meaning a lot of people will not be eligible to benefit. This also applies to donanemab. 'As long as everyone is fully informed of the advantages along with any disadvantages and can make an informed decision, I can't see any argument [against]'."

Patient population

11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	We are aware of results from the clinical trial showing differences in the effectiveness of donanemab in some populations. Most notably, people with lower levels of the protein tau were seen to benefit more. Whilst this is a clinical effectiveness matter, it does show that, in general, early treatment may be more effective. This underlines the vital importance of an early diagnosis. Supplementary data from the published results of the TRAILBLAZER-ALZ2 trial also show that the percentage slowing of decline of several cognitive measures is greater in women than in men. It additionally shows that the percentage slowing of decline of different measures is greatest in the white population compared to other ethnic or racial groups. However, the sample size of non-white participants is too small to make definitive judgements.

Equality

12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	Being eligible to receive donanemab relies on an early, accurate diagnosis, and we know there are inequalities in access to diagnosis. For example, people living in rural areas and people from ethnic minority backgrounds are less likely to have a diagnosis[31]. Levels of deprivation can also affect diagnosis rates. There is also regional variation in diagnosis rates from 50% to around 90% in different local authority areas[32]. Every effort needs to be made to reduce the likelihood of regional variation in access to DMTs, due to both variability in access to diagnosis but also variability in access to locations to receive treatment. As well as affecting diagnosis rates, dementia risk is increased with deprivation[3334]. People from a black ethnic background are also more likely to develop dementia than people from a white ethnic background[35]. Equality of treatment across all ethnicities is therefore vital. However, whilst the donanemab clinical trial study did include some participants from ethnic minority backgrounds, the participant group included in the trial was more than 94% white[36]. As such, it could be argued that we don't fully understand the effectiveness of donanemab in all minority ethnic groups. Another under-studied group is people with Down's Syndrome, who are more likely to develop Alzheimer's disease and will have amyloid clumps in their brains by the age of 40[3738]. Due to the age cut-offs of clinical trials, it is unlikely that many (if any) people with Alzheimer's disease and Down's Syndrome were enrolled on the trial. The low age cutoff of the TRAILBLAZER-ALZ 2 trials was 60 and it was suggested that there may be no one with Down's syndrome at 65 with early stage Alzheimer's disease[39]**.** This means that the effects of donanemab on this group of people needs proper investigation.

[31] Inequalities in dementia: unveiling the current evidence and developing measures to quantify them. Besley et al, 2023, publication forthcoming.
[32] https://digital.nhs.uk/data-and-information/publications/statistical/primary-care-dementia-data
[33] https://www.sciencedirect.com/science/article/pii/S0749379723000120
[34] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9971857/
[35] https://pubmed.ncbi.nlm.nih.gov/36223334/

[36] https://pubmed.ncbi.nlm.nih.gov/37459141/
[37] https://onlinelibrary.wiley.com/doi/abs/10.1002/ana.410170310?sid=nlm%3Apubmed
[38] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4678594/
[39] https://www.fiercebiotech.com/biotech/down-syndrome-and-alzheimers-pharma-clinical-trials-safety-lecanemab#:~:text=So%20far%2C%20no%20patients%20with%20Down%20syndrome%20in%20their%20medical%20histories%20have%20been%20enrolled%2C%20a%20spokesperson%20for%20Lilly%20confirmed.

Other issues

13. Are there any other issues that you would like the committee to consider?	Donanemab is one of the first disease-modifying treatments (DMT) for Alzheimer's disease capable of slowing down progression to be appraised by NICE. This makes it unique from all other current treatments for Alzheimer's disease available on the NHS. Approval of a DMT for Alzheimer's disease has the potential to be a catalyst for transforming diagnosis for dementia. The system change needed to prepare for delivery of a DMT includes increasing diagnostic capacity and access to specialist diagnostic tests to diagnose dementia subtype, which is crucial in order to access DMTs. This requires infrastructure changes as well as improvements in workforce capacity and skillset, which will be needed to improve access to an early diagnosis and to prepare for an increase in the number of people seeking a diagnosis in the event a DMT is approved for use. Improvements in diagnostic capacity will benefit not only people who are eligible to receive a DMT, but the wider population of everyone with dementia as well, which is vital given the challenges we have already outlined in terms of the number of people across England, Wales and Northern Ireland without a diagnosis and the care and support it brings. Without a diagnosis, people can't access treatments, information, advice and opportunities to participate in research. There is evidence of the benefits of diagnosis across a number of areas: it can enhance understanding of the impact of modifiable lifestyle factors on the disease process and the impact of interventions such as counselling[40]; it allows optimal medical management to delay progression and rule out other possible causes of symptoms [41]; it can support risk reduction[42] and it is associated with reductions in care giver burden, fear and anxiety.[43] There is significant work that needs to be done to deliver system change, but a DMT can act as a catalyst for this change. We know that work is underway on this; it is vital that this work is prioritised and takes place at pace so that the system is ready if a DMT is approved. Otherwise, we could face a situation where those technically eligible for treatment cannot access it because they don't have the diagnosis they need. Additionally, the prospect of a treatment that slows progression could challenge the perception that nothing can be done to support a person with dementia. We hear anecdotally from people worried about family members that some people are reluctant to seek a diagnosis, fearing that nothing can be done to help them. We also know anecdotally that some health and care professionals believe there is sometimes no point in diagnosing people with dementia due to the absence of disease-modifying treatments. Whilst we know that a diagnosis can benefit people in many ways, a disease-modifying treatment could help increase diagnosis rates by providing an additional benefit.

	It is important for NICE to consider the benefits of donanemab for unpaid carers as well as for people with Alzheimer's disease. As outlined earlier in our response, caring for someone with Alzheimer's disease has a significant impact on the health and wellbeing of unpaid carers, and the benefits to them of a drug which can delay increasing care needs of the person with Alzheimer's disease needs to be considered. It will be important to be clear in communication on donanemab about who will be eligible to receive the treatment. There is likely to be high interest in wanting to take the drug and it will need to be made clear who will not be eligible so as not to raise hopes of people who are not. We recommend that NICE ensure that the involvement of people living with Alzheimer's disease is central to the overall appraisal process. We recommend this in particular due to the challenges we experienced in obtaining evidence from people living with Alzheimer's disease in direct relation to donanemab for this submission.

[40] https://doi.org/10.3390/diagnostics6010006
[41] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2787842/
[42] https://doi.org/10.1002/14651858.CD006222.pub3
[43] https://www.tandfonline.com/doi/full/10.1080/13607863.2016.1179262

Key messages

14. In up to 5 bullet points, please summarise the key messages of your submission.	• **Alzheimer's disease impacts every area of people's lives,** from ability to communicate and socialise to mobility and independence. For many it can cause anxiety and depression, and in the later stages of disease progression will lead to people struggling with tasks of daily living. Ultimately, dementia will mean a person is increasingly reliant on social care and is likely to require residential care. • **There is a lack of support for people living with Alzheimer's disease with many people struggling to access the support that they need** to help them in their daily lives. People desperately want more support to help them live with the condition. • **Alzheimer's disease has a huge impact on the health and wellbeing of unpaid carers, with many reaching breaking point** due to their caring responsibilities and the lack of support available. • **People living with Alzheimer's disease want to be able to slow the progression of symptoms** to improve their quality of life, to have more time to live a 'normal' life, and to spend more time with loved ones. • **Approval of a DMT for Alzheimer's disease has the potential to be a catalyst for transforming diagnosis for dementia**. This is all-important given that at present, more than a third of people in England don't have a diagnosis and thus access to the information and support it can bring. A DMT could lead to healthcare system leaders increasing diagnostic capacity and improving access to an early diagnosis and subtype diagnosis, benefitting people by enabling them access to treatment where eligible, and other forms of support otherwise. The prospect of a treatment that slows progression could also challenge the perception among some that nothing can be done to support a person with dementia.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

Please select YES if you would like to receive information about other NICE topics - YES or NO

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NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Donanemab for treating mild cognitive impairment or mild dementia caused by Alzheimer's disease [ID6222]

Patient Organisation Submission

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type. [Please note that declarations of interests relevant to this topic are compulsory].

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

NICE National Institute for Health and Care Excellence

About you

1.Your name	[redacted]
2. Name of organisation	Dementia UK
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	Dementia UK is a specialist dementia nurse charity. Our dementia specialist nurses, called Admiral Nurses, who we continually support and develop, provide life-changing care for families affected by all forms of dementia. Admiral Nurses help families and carers to manage complex needs, by providing clinical support, care co-ordination and advocacy on behalf of people and their families. Clinical support from Admiral Nurses spans peri diagnosis through post diagnostic care, through pathway transitions, to end of life care and post-bereavement support. Their specialist support can help people living with dementia stay independent for longer – and ensure families are better supported in their caring role. Admiral Nurses also provide health and social care services with specialist advice and best practice guidance. For more information visit www.dementiauk.org Dementia UK receives no government funding, and the charity relies on voluntary donations that includes individual donations, corporate partnerships and gifts in wills. Dementia UK currently has 221 employees. We have over 70 Admiral Nurses on our Helpline; 24 of them are sessional staff and the rest are employees.
4b. Has the organisation received any funding from the company bringing the treatment to NICE for evaluation or any of the comparator treatment companies in the last 12 months? [Relevant companies are listed in the appraisal stakeholder list.] **If so, please state the name of the company, amount, and purpose of funding.**	No

4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
5. How did you gather information about the experiences of patients and carers to include in your submission?	Expertise of clinical staff within Dementia UK and dementia specialist Admiral Nurses and their contact with families affected by dementia through our Helpline and clinics has primarily contributed to information gathering. We have also gathered insights from people on our Lived Experience Advisory Panel (LEAP) about their personal experiences of Alzheimer's disease. Dementia UK has previously submitted a response to the Lecanemab appraisal. Given the similarity between the two drugs, much of our insights, questions and concerns are the same.

Living with the condition

6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	Alzheimer's disease is a condition characterised by significant variability, and individuals living with Alzheimer's disease undergo diverse and unique experiences. The most common early symptom of Alzheimer's disease is memory loss. Other early symptoms include mood changes, becoming withdrawn, difficulty with making decisions, and feeling unsettled by unfamiliar situations. Middle and later stages of Alzheimer's disease involve progression of these symptoms, as well as added challenges such as incontinence, difficulty with speech, delusions, and disrupted sleep. Alzheimer's disease is a progressive and life-limiting condition for which there is currently no cure. For many, receiving a diagnosis of Alzheimer's disease can instil fear and confusion, impacting not only the individual with the diagnosis but also those involved in their care, as well as their broader family and friends. Living with Alzheimer's disease can mean that day to day tasks require additional time, care and attention, as well as incorporating new processes to deal with memory deterioration. Individuals and their families may live with the condition for many years during which each and every day can throw up new and complex challenges as symptoms progress and individuals and their families try to navigate a complex and disjointed health and social care system. Trying to support someone with Alzheimer's disease can be exhausting and overwhelming. It is easy for family carers to become socially isolated as they put their own lives on hold and can often experience a severe deterioration in their own health and wellbeing.

Current treatment of the condition in the NHS

7. What do patients or carers think of current treatments and care available on the NHS?	As noted within the final scoping document, there is no cure for Alzheimer's disease and there are currently no disease modifying treatments approved for use in the UK. For mild cognitive impairment, there are only non-pharmacological approaches, such as delivered through social care, primary and community health services, and information and advice services. For dementia caused by Alzheimer's disease, pharmacological options are limited, and as such there is also a large dependence on non-pharmacological options. Those with lived experience of Alzheimer's disease have informed us that the currently available pharmacological options currently seem 'unimaginative', and also noted a lack of cognition protection or enhancement interventions (interventions, pharmacological or non-pharmacological, to slow or mitigate the decline of cognitive functions). For both mild cognitive impairment and dementia due to Alzheimer's disease, GPs are usually the 'first port of call' in seeking a diagnosis but also following discharge from memory services, where individuals with the diagnosis will be referred back to primary care services. However, our experience from contact with people with dementia and their families, is that non-pharmacological support is often lacking in quality, accessibility, co-ordination, and timeliness. Those affected by dementia are often unaware of what support is available, and it can be extremely difficult to access support, with many people with the diagnosis and their families falling between the gaps between health and social care. Support that is provided is often fragmented and not joined up, with frequently poor communication and integration between key service providers. Furthermore, much of this support is unavailable on the NHS, with people with dementia often not deemed eligible for NHS Continuing Healthcare (CHC) funding due to a lack of recognition of the complex needs associated with a diagnosis of dementia. Furthermore, the support that is available on the NHS, such as signposting to further support providers and statutory services, often does not happen in practice due to the strain on NHS services or limited availability of services locally.

8. Is there an unmet need for patients with this condition?	There is a large degree of unmet need among people with Alzheimer's disease, and their families and carers. Non-pharmacological interventions and support are often difficult to access, fragmented, and limited in scope, if it is available at all. There are no disease modifying treatments currently approved for use in the UK. There are no pharmacological treatments for managing mild cognitive impairment due to Alzheimer's disease and limited pharmacological treatments for managing dementia due to Alzheimer's disease. Thus, unmet needs involve both health and social care needs of the individual and their families. Examples of this include family carers struggling with managing complex behaviours such as aggression and sexualised behaviours, having limited or impersonal care which fails to meet the needs of the individual, and a lack of emotional support for people with dementia and carers who are struggling to cope and experiencing mental health complications. Furthermore, there is currently no unique pathway for dementia care, so people in many localities frequently struggle to understand what is available for them as the condition progresses. Unmet need can lead to avoidable crisis situations and carer breakdown which can increase the risk of hospital admissions and moves into long term residential care for the person with dementia and both physical and psychological ill-being for family carers.

Advantages of the technology

9. What do patients or carers think are the advantages of the technology?	Given the impact of Alzheimer's disease on individuals and their loved ones as outlined above, people with lived experience of Alzheimer's disease stated the main advantages of a disease modifying treatment, such as Donanemab, to be the slowing of the progression of the Alzheimer's disease and improved management of symptoms. Although many people with Alzheimer's disease can have a good quality of life, especially with appropriate health and social care support, many of the characteristics of cognitive impairment caused by Alzheimer's disease of any severity can be upsetting, frustrating and stressful, and impede the individual's ability to carry out day-to-day tasks. Furthermore, Donanemab provides opportunity for an individual to self-manage their condition for longer, with less dependence on carer input, which provides more control over their life. The potential for Donanemab to promote independence and prolong time living at home would help people living with the condition to make home and lifestyle adjustments and plan ahead, thereby also potentially reducing the financial burden of Alzheimer's disease on the NHS. The potential for a slower progression of complex behavioural and cognitive needs could lessen stress and anxiety for carers, thus reducing strain on carers own health and wellbeing, and enabling them to better balance caring with other responsibilities such as work. Slowing the progression of Alzheimer's disease would likely also allow for more time for future planning, enabling the person with Alzheimer's disease and their families to get their financial affairs in order and make decisions about their future care. Those with lived experience of Alzheimer's disease have stated that Donanemab would provide hope for those eligible and would also help 'hold the fort' while other treatments are developed.

Disadvantages of the technology

10. What do patients or carers think are the disadvantages of the technology?	According to those with lived experience of Alzheimer's disease, the key disadvantage to Donanemab is the negative side effects and safety concerns, ranging from dizziness to brain bleeds. As such, there will have to be close monitoring of those on Donanemab to observe for and address any side effects, especially brain bleeds. Sector research with people and carers has highlighted that this monitoring will be a concern for some people, due to the additional time required, and because monitoring can be a frightening or stressful experience. Likewise, those with lived experience of Alzheimer's disease have noted that the route of administration could be a disadvantage, as an intravenous administration every four weeks could likely be a significant time, emotional and financial burden. Similar to monitoring, this is likely to be frequently stressful and time consuming. Needing to go to a clinic every four weeks will require additional planning and organisation, for the person with Alzheimer's disease and/or their carers. This might also be a particular disadvantage for those who are low income due to the costs of travel, hospital parking, and time off work. Furthermore, the MRI or PET scans required for diagnosis, and intravenous treatment, can be uncomfortable or painful; especially given clinicians may be less confident in the administration of this intervention, as it is new to this field of practice. There is also potential for disappointment and distress for people affected by Alzheimer's disease, whose cognitive impairment is too severe to benefit from the technology (i.e., individuals who have entered the moderate to advanced dementia stage of Alzheimer's disease). Dementia UK recommends that there is careful consideration of how the cut-off point for eligibility for the technology is communicated and understood, and that a holistic approach is taken across a wide variety of stakeholders who are responsible for sharing this communication. On an ongoing basis, it is important to communicate to patients who are eligible, and their carers, that observable changes at the individual level occur amidst a continuous cognitive decline and that the average treatment effect may not be perceptible or vary on an individual basis. Information and advice should be built into carer and patient educational programmes, such as START, to better inform families on issues involved in its administration. Furthermore, there should be clear communication about the fact that at some point in the condition's progression the drug may no longer be effective. Those with lived experience of Alzheimer's disease have said that anxiety about the drug being taken away from them before they feel ready is a cause for concern. Thus, it is also important that non-pharmacological, post diagnostic support interventions are still sufficiently scrutinised, adapted and improved, as these will remain crucial for the quality of life for the vast majority of people living with Alzheimer's disease, especially those where it has progressed beyond when Donanemab can be effective. It is also vital that other pharmacological options, that do not focus on clearing Amyloid, are also still given due funding and consideration.

Patient population

11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	It is expected that the main beneficiaries will be those with very early diagnosis, where there is sufficient time to be tested, assessed and administered with Donanemab. Those who are living independently with a timely diagnosis might well benefit the most, as receiving Donanemab may significantly extend their independence and prolong their ability to self-manage. That being said, where capacity and insight are lost early due to Alzheimer's disease, the intervention may cause distress due to the invasive nature of the administration. As stated previously, those with advanced Alzheimer's disease will not benefit due to their lack of eligibility and they and their families may well experience disappointment and distress at not being able to receive this treatment. As noted in the Equality Impact Assessment, people with mild dementia or mild cognitive impairment due to Alzheimer's disease are not routinely tested for amyloid pathology in the NHS; amyloid testing is required so that doctors are able to tell who is eligible for treatment. The dependence upon such tests may well exacerbate inequalities when it comes to accessing Donanemab, as diagnosis rates are unequal across certain demographics. In addition to marked regional differences in dementia diagnosis rates, there are underlying structural and cultural inequities in the recognition of symptoms and provision of care among diverse populations. This suggests that marginalised and under-served groups may be less likely to benefit. For instance, a 2018 study found that black people within the UK appear to be more at risk of dementia but less likely to receive a timely diagnosis[i]. Additionally, research indicates that people of South Asian heritage within the UK are more likely to receive a dementia diagnosis at a later stage[ii]. An additional group of people thought to be at risk of underdiagnosis is the prisoner population. Some estimates have suggested that dementia prevalence is higher within prisoners than the general population.[iii] However, due to a lack of training on dementia for staff, and a lack of screening and poorer quality healthcare, dementia remains underdiagnosed within the prisoner population. Similarly, those with young onset dementia are statistically less likely to receive timely diagnosis than people with dementia over the age of 65: the average time to diagnose is 4.4 years in younger people compared to 2.2 years for people aged over 65. However, as noted in the Equality Impact Assessment, Young Onset Alzheimer's disease has an increased chance of having amyloid pathology confirmed, and those affected are less likely to die of other conditions meaning they are more likely to see longer term benefits. Yet Donanemab has not yet been tested on those with Young Onset Alzheimer's disease specifically, for additional/different benefits and side effects. As such, we approve of the decision for further, separate examination of people living with Young Onset Alzheimer's disease with regards to Donanemab.

Equality

12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	To address the disparities mentioned above, it is essential to explore ways in which groups facing these challenges can access the technology. This involves considering the necessary provisions such as cognitive screening programmes to encourage diagnosis and early help-seeking, ensuring that individuals initiate the treatment pathway at an appropriate stage in the progression of their symptoms. As noted in the Equality Impact Assessment, it is also important to monitor for differential responses to Donanemab across different ethnic groups and those with Young Onset Alzheimer's disease.

Other issues

13. Are there any other issues that you would like the committee to consider?	To successfully implement Donanemab in NHS healthcare settings, it is crucial to significantly enhance system preparedness, training, and resources, as currently there is not sufficient capacity to roll out this treatment in an equitable manner. As Donanemab is only provided to those with mild to moderate cognitive impairment due to Alzheimer's disease, it is vital that there are improvements to timely diagnosis. Although NHS England has set out ambitious targets in respect to the diagnosis rate, people still routinely wait for months to access primary care appointments, diagnostic tests and support with the diagnostic process, causing long, undue delays for diagnosis. This is an issue above and beyond access to Donanemab; those with lived experience of having an early diagnosis of Alzheimer's have said that a timely diagnosis enabled them to access necessary support, such as peer support networks. As stated above, there are also lower diagnosis rates among different demographics, such as those with Young Onset dementia or those living in rural areas. This issue is part of far broader capacity problems within primary care. Additional infrastructure will also be required for testing of amyloid pathology, which is currently not routinely tested for, which would put additional strain upon NHS systems and resources. Furthermore, as Donanemab is to be administered intravenously every four weeks, availability of suitable settings, as well as skilled staff to carry out the treatment, could be a barrier. Follow ups and reviews for those on Donanemab would also add to strain upon NHS capacity. This situation thus raises two major concerns: ensuring equitable provision of the necessary infrastructure, particularly between urban and rural/remote settings or within socio-economically

	deprived areas and evaluating the capability of the existing dementia workforce to deliver this treatment. Improving system preparedness, and signposting to key services, is necessary to prevent the widening of existing inequalities. In light of these challenges, we urge NICE to consider system preparedness when making recommendations, providing guidance on how to ensure fair access to this treatment without exacerbating inequalities. Additionally, we request that there is scrutiny of how access to Donanemab will be monitored and reported, considering geographical, socio-economic, and protected characteristics. We also urge there to be broader consideration of how, if amyloid pathology testing is expanded, the NHS will cope with a large influx of Alzheimer's disease diagnoses and provide support beyond access to Donanemab. Indeed, broader post diagnostic support must remain a priority, as Donanemab will only benefit a minority of those with Alzheimer's disease, which is only one form of dementia among many. It is vital that other forms of dementia do not lose out comparatively, due to the implementation of Donanemab requiring additional financing and resources. Dementia UK also urges that patient and carer perceptions and experiences of the Donanemab treatment and effectiveness be gathered and considered when assessing the clinical benefit of Donanemab. The value placed by the individual and their family on the change depends on various factors, including individual differences and contextual elements such as the severity of the disease. Examining the individual's value of an effect adds clarity to the assessment, as each individual account can build a broader picture of effectiveness. Similarly, it is crucial to consider functional and quality-of-life outcomes alongside core symptomatic scales, as Alzheimer's disease is a highly complex, life-limiting disease with diverse impacts, frequent co-morbidities, and impacts beyond the person with Alzheimer's disease (i.e., on their family carers). This comprehensive approach is necessary as the intervention may have a positive but non-specific effect, such as on sleep or appetite, potentially enhancing function or quality of life without directly addressing specific symptoms of Alzheimer's disease. To gauge the value of a change at different disease stages, additional outcome measures become relevant, including the impact on carers, behavioural and psychological symptoms, as well as longer-term considerations such as life expectancy and the likelihood of long-term residential care. Dementia UK therefore welcomes the inclusion of health-related quality of life measures within the final scoping document. However, Dementia UK would encourage carer quality of life outcomes to be as specific as possible. Dementia UK would also like clarification as to how long eligible persons will be on Donanemab for, and how this will be communicated. We also wish to stress the importance of considering co-morbidities and polypharmacy during assessment, as these are both common among people with Alzheimer's disease. Dementia UK is also interested in how benefits and side effects of Donanemab will be monitored among those with Young Onset Dementia specifically.

Key messages

14. In up to 5 bullet points, please summarise the key messages of your submission.	• Donanemab could bring hope, and improvements to the quality of life for those with mild to moderate Alzheimer's disease. • However, the NHS does not currently have the capacity to roll out this treatment in an equitable manner. How equality of access to Donanemab can be achieved should therefore be carefully considered. • Communication around who is eligible for Donanemab should be carefully considered. • Patient evaluation of the change, as well as broader quality of life outcomes, should be taken into consideration. • Pharmacological options are currently at best limited for those with mild cognitive impairment and dementia caused by Alzheimer's disease. As such, alongside a decision on Donanemab, non-pharmacological post-diagnostic support must be integrated, and remain a priority, within clinical pathways.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

Please select YES if you would like to receive information about other NICE topics - YES or NO

For more information about how we process your personal data please see our privacy notice.

[i] NHS Bristol, North Somerset and South Gloucestershire (2022). ADAPT: The south Asian Dementia diagnosis pathway - an online toolkit of enhanced interventions - NHS BNSSG ICB. [online] NHS. Available at: https://bnssg.icb.nhs.uk/about-us/research-and-evidence/our-research-portfolio/previously-supported-projects/adapt-the-south-asian-dementia-diagnosis-pathway-an-online-toolkit-of-enhanced-interventions/#:~:text=South%20Asian%20people%20are%20more%20likely%20to%20be.

[ii] Dementia UK (2023). Young onset dementia: facts and figures. [online] Dementia UK. Available at: https://www.dementiauk.org/information-and-support/young-onset-dementia/young-onset-dementia-facts-and-figures/.

[iii] Purewal, R. (2020). Dementia in UK prisons: Failings and solutions? *Criminal Behaviour and Mental Health*, [online] 30(2-3), pp.59–64. doi:https://doi.org/10.1002/cbm.2150.

NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Donanemab for treating mild cognitive impairment or mild dementia caused by Alzheimer's disease [ID6222]

Professional organisation submission

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 13 pages.

NICE National Institute for Health and Care Excellence

About you

1. Your name	[redacted]
2. Name of organisation	Association of British Neurologists
3. Job title or position	[redacted]
4. Are you (please select Yes or No):	An employee or representative of a healthcare professional organisation that represents clinicians? **Yes** or No A specialist in the treatment of people with this condition? **Yes** or No A specialist in the clinical evidence base for this condition or technology? **Yes** or No Other (please specify):
5a. Brief description of the organisation (including who funds it).	The aim of the Association of British Neurologists is to promote excellent standards of care and champion high-quality education and world-class research in neurology. The ABN's principal objectives are to: • Encourage nationwide availability of excellent and equitable neurological services • Support neurologists and neurological trainees in their clinical practice • Support neurologists and neurological trainees in their research and academic activities • Increase knowledge of the nervous system and its disorders • Ensure the continuing professional development of its members. • Promote the education of neurological trainees and support learning of neurology throughout medical training • Collaborate with the Royal College of Physicians (London, Edinburgh and Glasgow). • Foster communication with patient interest groups. • Maintain contacts with neurologists in developed and in developing countries. • Provide guidance when required for matters relating to neurology and standards in clinical practice.

5b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.] **If so, please state the name of manufacturer, amount, and purpose of funding.**	TBC by ABN – any funding from Eli Lilly?
5c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No

The aim of treatment for this condition

6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	Prevent progression of cognitive decline and/or improve symptoms
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	Longer term (e.g. over 1-10 yrs) • In mild cognitive impairment (MCI) due to Alzheimer's disease – to prevent or significantly delay progression to dementia over time • e.g. operationalised as Clinical Dementia Rating (CDR) change from 0.5 to ≥1 • In mild AD to prevent or significantly delay progression to dependency (i.e. care support/nursing home) Short term (e.g. over months to 1 year): • Change on a cognitive score/functional score consistent with meaningful improvement/slowing of decline, e.g. slowing of decline of about 30% in functional or quality of life measures might be a useful benefit for individuals if associated with absolute changes on clinical rating scales that meet minimal clinically important difference (MCID) thresholds • Or change in a biomarker (e.g. amyloid load) to control levels if subsequently shown to predict outcome
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Unequivocally yes. Current medication provides small cognitive improvement at best with no evidence for disease modification

What is the expected place of the technology in current practice?

9. How is the condition currently treated in the NHS?	• Treatment with cholinesterase inhibitors first line; memantine second line; combinations in some – symptomatic not disease modifying • Otherwise management is supportive or palliative
9a. Are any clinical guidelines used in the treatment of the condition, and if so, which?	• NICE guidance for dementia diagnosis (NG97) • Midlife approaches to prevention (NG16) • Technology assessment (TA217) – cholinesterase inhibitors and memantine
9b. Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	• The pathway of care is to receiving a dementia diagnosis is generally via community memory services with some patients being seen in neurology-led cognitive clinics. National memory service audits show significant variation in every aspect of diagnostic practice.The pathway is made more complex as there is poor integration between memory services and neurology-led services, little evidence of joint working and variable access to neuroradiological expertise. Diagnostic practice varies enormously with some specialist centres providing molecular diagnostics (routinely, or in selected cases), while access to and ability to interpret biomarkers is extremely limited in memory services. The range ofmultidisciplinary diagnostic and support services varies very significantly across the country, often as a result of insufficient resource. • Inconsistent uptake of guidance for primary care diagnosis of dementia e.g. DiADeM • Inconsistent pathway for patients to flow between secondary (community memory services) and tertiary (neurology-led specialist clinics) care • No guidance for management of Mild Cognitive Impairment (MCI) • Variable use of diagnostic technology even within NICE framework • In addition to the pathway variation, there are wide ranging views on how to manage diagnosis and on what assessments are appropriate.

9c. What impact would the technology have on the current pathway of care?	• Would fundamentally change, with the potential to greatly improve the current pathways and promote equity of access to diagnosis and management. • Likely to significantly increase patients presenting to cognitive services. • Would require clear guidance for approach to diagnosis of MCI. • Would clarify pathway flow including criteria for specialist service referral • Would require clarification on thresholds for referral for diagnostic testing • Would require upscaling of biomarker use for diagnostic testing (amyloid PET/CSF and MRI) and monitoring (MRI) in clinical practice (i.e. outside of specialist centres and clinical trials). Blood based biomarkers are likely to eventually supersede these either for screening or as entry criteria, but requisite evidence is not yet in place. • Would necessitate expansion in capacity and capability of drug delivery via infusion and in the monitoring, diagnosing and managing complications
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	• Currently no drug infusion licenced for use for dementia so no current care pathway exists for this type of treatment. Similar models are, however, used in NHS practice for other conditions (e.g. multiple sclerosis, immune modulation in rheumatology) • Diagnostic tools used in some centres but not widely incorporated into clinical practice • MRI/CSF recommendations as per NICE guidance are in place in some but not all centres • Amyloid PET in very few centres, and very limited experience in clinical pathways outside of research trials • Implementation will require a dramatic change in the resourcing of diagnostics and in education in interpretation across the pathway.
10a. How does healthcare resource use differ between the technology and current care?	This would be a major step change, requiring healthcare resources for: • Education to upskill patients, primary care referrers, eligibility decision-making, outcomes evaluation and in monitoring safety • Improved molecular diagnostics – personnel to deliver (e.g. CSF/PET) and interpret • Facilities to perform relevant investigations (PET radiotracer/scanners; CSF suites etc) • Delivery of treatments (pharmacy, infusion suites, reporting) • Imaging capacity for monitoring post treatment (routine) and if complications (unscheduled, urgent) • Pathway integration and capacity to manage diagnostic and drug side effects (e.g. post-LP headache, brain oedema & microhaemorrhage)

10b. In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Initially likely to be in secondary/tertiary specialist centres with access to appropriate diagnostic, infusion and monitoring support/expertise. A regional network would be required and clear criteria for referral; over time local centres would be trained and upskilled to democratise diagnosis and management where possible.
10c. What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	Investment would be required for the following: • Education to upskill patients, primary care referrers, eligibility decision-making, outcomes evaluation and in monitoring safety • Improved molecular diagnostics – personnel to deliver and interpret CSF/PET biomarkers • Introduction of ApoE4 genetic testing (with appropriate pre and post-test counselling) in clinical settings to identify those at highest risk of adverse events • Facilities to perform relevant investigations (PET radiotracer/scanners; CSF suites etc) • Delivery of treatments (pharmacy, infusion suites, reporting) • MR imaging capacity for monitoring post treatment (routine) and if complications (unscheduled, urgent) • Pathway integration and capacity to manage diagnostic and drug side effects (e.g. post-LP headache, brain oedema & microhaemorrhage)
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	• The mode of action of Donanemab is clearance of A-beta plaques from the brain, with the aim of attenuating the pathological processes that are thought to be downstream, including neuroinflammation and neurodegeneration. As neurodegeneration is associated with cognitive decline, the aim is to slow or halt the progression of cognitive decline, e.g. from MCI to dementia; or from mild dementia to more advanced stages. • The results of the pivotal phase 3 study (https://jamanetwork.com/journals/jama/fullarticle/2807533) showed that treated patients had statistically significantly attenuated rates of cognitive decline over 18m both in the primary outcome (iADRS) but also on a range of other cognitive outcomes. It is hoped that the differences between treated and untreated patients will continue to increase beyond the duration of the study, i.e the trajectory of cognitive decline will alter over much longer time frames, although there is a high degree of uncertainty about this. There are differing views within the profession as to whether the demonstrated benefits are clinically meaningful. • There are differing views within the profession as to whether the demonstrated benefits are clinically meaningful or meet the generally accepted minimal clinically important difference (MCID).

11a. Do you expect the technology to increase length of life more than current care?	See response above. Good reason to expect improvements in health-related quality of life rather than length of life per se although these are also possible with maintained function and reduced frailty.
11b. Do you expect the technology to increase health-related quality of life more than current care?	See response above.
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	• Individuals covered by the inclusion criteria in the clinical trials – MCI and mild AD with evidence of brain beta-amyloid – are most likely to benefit. • It is less likely that individuals with more advanced dementias will benefit. • The clinical trials suggest that there may be differences in response and side-effects in individuals with ApoE4, and current appropriate use recommendations suggest routine ApoE4 testing (not currently available in clinical settings) to help guide safe use • To date individuals in the clinical trials have had relatively "pure" AD. It is not yet clear to what extent the presence of major cerebrovascular disease (or its subtypes), other comorbidities or use of other drugs (e.g. anticoagulants) will influence outcomes and side-effects in routine clinical practice.

The use of the technology

13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient	This technology will present major challenges to delivery, as outlined above (see replies to 10) In brief this will require a major implementation plan coordinated at national and regional level including issues related to patient identification and selection; diagnostic access – clinical and biomarkers; supply and delivery of drug; monitoring for side-effects, efficacy and termination of treatment; and management of patient and societal expectation.

acceptability or ease of use or additional tests or monitoring needed.)	Specific implications: • additional diagnostic testing (to identify disease markers) • decision-making around who to send for testing • additional monitoring (regular MRI) and follow-up visits to assess efficacy/outcomes
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Yes – testing at each stage (diagnosis, monitoring during treatment) as indicated Entry criteria – demonstration of amyloid pathology (CSF/PET); MRI Monitoring – MRI + expert neuroradiology interpretation Stopping – criteria as yet unclear; likely to include biomarker testing
15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	The longer-term effects of this drug are as yet unclear. As a disease-modifying agent, it would be expected to delay conversion from MCI to AD (i.e. maintain independence); and increase time to nursing home admission/dependency. This would be expected to result in substantial savings in: • health and social care costs (resource use);

	• to influence the patient's QoL as assessed by both individuals and carer; and • importantly also the QoL of the caregiver(s) noting that Alzheimer's disease impacts hugely not just on patients' QoL but (and often more) the QoL of their carer/families However, all of these long term predictions are associated with a high degree of uncertainty.
16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	Yes. Depending on the long-term outcomes of a post-surveillance trial there is large potential for impact in all these areas. There is further potential to consolidate and standardise approaches to diagnosis and management within clinical pathways for dementia (indirect impact).
16a. Is the technology a 'step-change' in the management of the condition?	Potentially yes (see above)
16b. Does the use of the technology address any particular unmet need of the patient population?	Yes – Alzheimer's disease is a huge unmet need. Use of an effective disease-modifying drug in this condition would be expected to reduce dependency and delay institutionalisation which would significantly address patient population need.
17. How do any side effects or adverse effects of the technology affect the management of the	MRI brain changes (Amyloid Related Imaging Abnormalities, ARIA) were seen in 24% of individuals in the clinicals trial on MRI. The majority of these were asymptomatic. However, a 6% percentage of patients had symptomatic ARIA and in 1.5% this was judged a serious adverse event e.g., causing

condition and the patient's quality of life?	hospitalisation. Outcomes of patients who developed symptomatic ARIA (e.g., the proportion with significant worsening of dementia or permanent neurological disability have not been published. Three deaths attributable to Donanemab occurred during the trial. Individuals on this treatment will require regular MRI surveillance and interpretation and clinical management where symptoms occur. This will in turn require training of neuroradiologists on the often subtle features of ARIA, and of nursing staff on the nonspecific symptoms, and when to escalate. The impact on QoL for individuals is unclear, but it is expected that when given in line with the trial entry criteria significant problems will only be seen in a small minority. However, this depends on the marketing authorisation. If this is more permissive that the trial criteria, then it is likely that when transferred to a real-world population the incidence of ARIA will be higher due to less stringent exclusion of patients with cerebrovascular disease.

Sources of evidence

18. Do the clinical trials on the technology reflect current UK clinical practice?	No. There are large numbers of patients with MCI and AD who would fall within the entry criteria for the relevant clinical trials. Few patients receive the diagnostic work-up mandated by clinical trial protocols as NICE guidance suggests AD biomarkers only in diagnostically challenging cases and most memory services lack access to CSF biomarkers.

18a. If not, how could the results be extrapolated to the UK setting?	Clinical trial results will require a change to standard practice in dementia diagnosis and treatment in the UK. This represents a paradigm shift in the approach to dementia management, however the results of clinical trials can be extrapolated by utilising appropriate selection criteria of patients for therapy. This is currently performed in some, but not all, clinical settings.
18b. What, in your view, are the most important outcomes, and were they measured in the trials?	Donanemab has demonstrated significant attenuation of decline in cognition and daily life function, as well as clear evidence for disease modification (amyloid removal). These are the most important outcome measures. Whether the size of effect as demonstrated is clinically meaningful is a current topic of debate.
18c. If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	There are theoretical reasons to suggest that removal of amyloid (as shown in this study) should have impact on downstream markers of neurodegeneration and a sustained downstream effects on cognition, but evidence to support this at the present time is limited
18d. Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	N/A
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
20. Are you aware of any new evidence for the comparator treatment(s)	No

since the publication of NICE technology appraisal guidance TA217	
21. How do data on real-world experience compare with the trial data?	Not yet available

Equality

22a. Are there any potential equality issues that should be taken into account when considering this treatment?	There are already marked discrepancies between diagnosis rates, use of biomarkers, and referral to specialist services for patients with dementia around the country, and in different socio-economic groups. These discrepancies are likely to influence who this drug is offered to, and there is a risk of exacerbating existing health inequalities, but also an opportunity to improve and level up services.
22b. Consider whether these issues are different from issues with current care and why.	Delivery of this drug requires careful investigation, selection, access to biomarkers and close monitoring. Whilst many of these aspects are considered best practice, they are not mandatory for delivery of current care; this will need to change to safely and equitably deliver this drug,

Key messages

23. In up to 5 bullet points, please summarise the key messages of your submission.	• Donanemab is a member of a new class of treatment for AD with evidence for disease modification, i.e. altering the course of the disease. • The evidence available to date shows that the drug has fundamental effects on core pathological features of Alzheimer's disease (removal of amyloid plaques) and statistically significant impacts on a range of cognitive outcomes. These might be associated with long term benefits in terms of delayed conversion from MCI to dementia; and from independency to dependency and admission for institutional care, although these predictions are associated with a high degree of uncertainty • The advent of a disease modifying drug for dementia provides a significant opportunity to make a step change in the provision of care for patients with MCI and mild AD, akin to the improvements seen following coordination of stroke services following the licence of thrombolysis. • This would require major investment multiple levels in the patient pathway from patient identification, assessment, investigation, drug delivery and monitoring • A large post-market surveillance study to establish the longer-term benefits is required and may be an appropriate way to allow patients in the UK access to treatment.

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NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Donanemab for treating mild cognitive impairment or mild dementia caused by Alzheimer's disease [ID6222]

Professional organisation submission

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 13 pages.

NICE National Institute for Health and Care Excellence

About you

1. Your name	[redacted]
2. Name of organisation	Faculty of Public Health
3. Job title or position	[redacted]
4. Are you (please select Yes or No):	An employee or representative of a healthcare professional organisation that represents clinicians? No A specialist in the treatment of people with this condition? No A specialist in the clinical evidence base for this condition or technology? Yes Other (please specify):
5a. Brief description of the organisation (including who funds it).	The Faculty of Public Health is a membership organisation for public health professionals across the UK and around the world. It is funded by membership and examination fees, educational conferences, charitable donations, and investment income.
5b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.] **If so, please state the name of manufacturer, amount, and purpose of funding.**	No
5c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No

The aim of treatment for this condition

6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	Donanemab and other amyloid immunotherapy agents aim to remove amyloid pathology from the brain in the hope that this will slow the progressive cognitive and functional impairment seen in clinically diagnosed Alzheimer's disease (which was defined in the trials as mild cognitive impairment attributed to Alzheimer's disease or mild Alzheimer's disease–related dementia on the basis of the US National Institute on Aging–Alzheimer's Association criteria). It is hoped that this in turn will lead to a slowing in the loss of quality of life (of both patient and caregiver(s)), and a reduction in some associated health and social care costs (e.g. by delaying the requirement for nursing home admission).
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	In terms of cognitive endpoints of trials, the best summary of this evidence is from *Liu et al., The need to show minimum clinically important differences in Alzheimer's disease trials. The Lancet Psychiatry. 2021.* (and is further discussed in *Liu et al., Evaluation of clinical benefits of treatments for Alzheimer's disease. The Lancet Healthy Longevity. 2023*) The best available evidence suggests estimates for the minimum clinically important difference in mild cognitive impairment (MCI) to be 0.98 for CDR-SB and 1.26 for MMSE. For mild Alzheimer's disease, the estimates increase (in recognition of the faster rate of decline at later phases) to 1.63 for CDR-SB, and 2.32 for MMSE. It is important to recognise the limitations of this literature. These measures are based on clinicians' views of clinically meaningful change in their patients. These clinical assessments should be holistic and consider the experiences of patients and their caregivers, but the measures do not account for these important perspectives directly. However, it is widely accepted that we need something beyond statistical significance to evaluate clinical meaningfulness of treatments, and the above represent the best available evidence. As recognised in the final scope for this evaluation, it is important to consider a full range of outcomes relevant to patients, caregivers and health systems, many of which lack evidence from the existing trial data and its short duration.

8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes. Current therapeutic options are limited, and produce small, symptomatic benefits for some patients. There is an unmet need for truly disease-modifying drugs which meaningfully slow the rate of cognitive and functional decline improving quality of life, with acceptable side effect profiles, and affordable financial and resource requirements. This requires understanding of what 'disease' means in this context, given the challenge being addressed is the dementia syndrome, with the diversity of our populations, age, gender, ethnicity being important aspects. The unmet need must be articulated clearly, therefore, as those whose dementia is clearly underpinned by amyloid pathologies alone in the brain are not the majority of those who develop dementia in our ageing populations.

What is the expected place of the technology in current practice?

9. How is the condition currently treated in the NHS?	Clinically diagnosed Alzheimer's disease, usually diagnosed on the basis of clinical picture and natural history is detected, diagnosed and managed in a variety of different settings from primary care, memory clinics, old age medicine, psychiatry, neurology, palliative care, social care and care settings. Clinical pathways aim to exclude reversible pathologies, manage co-occurring vascular risk factors and pathology, and offer symptomatic treatments (acetylcholinesterase inhibitors and memantine).
9a. Are any clinical guidelines used in the treatment of the condition, and if so, which?	NICE Guideline, NG97.
9b. Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	The clinicians based in the settings listed in Q9 who detect and manage clinically diagnosed Alzheimer's disease see a different profile of people, as the 'filters' to such settings determine the likely profile of the patients. This is not necessarily due to poorly defined care pathways; in large part this represents the true complexity of the dementia syndrome in the population. This can range from young onset with early manifestation of psychiatric symptoms but otherwise relatively fit, to (much more commonly) older and/or very frail with multiple conditions, to the end of life period. As described by *Brayne & Davis. Making Alzheimer's and dementia research fit for populations. The Lancet. 2012,* professionals may vary in their opinions depending on the nature of those at risk of or with dementia that they see in their clinical practice or that they research and recruit.

9c. What impact would the technology have on the current pathway of care?	It seems impossible for any roll out of donanemab not to have a major effect on the health system because of the sheer scale of resources required. The exact impact would depend on to whom the treatment would be offered. Eligibility for treatment could be restricted to those who match trial eligibility criteria (i.e. those that had mild cognitive impairment or mild AD at presentation with evidence of amyloid and tau pathology on PET scan, minimal/no other neuropathology on MRI scan, and no significant co-morbidity). Most people presenting to memory services would not meet these criteria - a US population-based cohort study found that of those with MCI or mild dementia and increased amyloid on PET, only 8% and 5.1% would meet the lecanemab and aducanumab trial eligibility criteria, respectively (this analysis was performed before the phase III donanemab trial results were published, and donanemab was therefore not included. But as the donanemab eligibility criteria were similar to that of the aducanumab and lecanemab trials, the results can be assumed to generalise) (*Pittock et al. Eligibility for Anti-Amyloid Treatment in a Population-Based Study of Cognitive Aging. Neurology. 2023*). Not all people with dementia attend memory services. Even less of the total population with dementia (e.g. including those presenting through old age medical settings) would meet eligibility criteria. Even in this scenario of tightly defined eligibility criteria, in which the number ultimately eligible would be low, many more would seek assessment for eligibility. The process and systems required to measure the biomarkers in all those seeking treatment to determine their ineligibility would consume significant resource. Many of the exclusion criteria for treatment (e.g. co-neuropathology on MRI scan), which are very common in the older population, cannot be confirmed unless scanning is undertaken (i.e. the resource would be needed, beyond clinical judgement, to confirm ineligibility). In a system already often struggling to provide proactive, high-quality, person-centred care to people with dementia in an equitable manner, this would present a significant opportunity cost. Consideration would also be due for the upset caused to the large majority who would be told after screening that they were ineligible for the new, much-hyped treatment. All those putting themselves forward would need to be counselled before any detailed imaging and other biomarker evaluation, possibly including lumbar punctures (with associated risks of side-effects which, although small, would accrue across large numbers). Age, gender, socioeconomic status, and co-morbidities all would be relevant factors. Genotyping is another consideration – the US Food and Drug Administration (FDA) drug label for another amyloid immunotherapy drug, lecanemab, includes the warning that the risk of the side effect amyloid-related imaging abnormalities (ARIA) is higher in APOE ε4 homozygotes (mentioned in the final NICE scope as a relevant subgroup, potentially excluded therefore). If donanemab is approved by the FDA, then the

	drug label is likely to feature the same warning given the results in the donanemab trial were consistent with those of the lecanemab trial. If deemed necessary prior to consenting for treatment, the resource implications may need to include genetic counselling, itself problematic and not routinely considered at present. Moreover, those who are APOE-4 homozygotes would receive double bad news - their prognosis is poorer and they are likely to be ineligible for the treatment. For those determined to be eligible, a new treatment pathway would need to be created that funded and facilitated infusions every 4 weeks delivered by specialist teams, almost certainly requiring specialist centres – with implications for the amount of travel and time commitment to which patients and caregivers would need to be able to commit (and in turn this will have effects on equity of access as those from more disadvantaged backgrounds will typically find this more difficult). A responsive system to cope with side effects would need to run in parallel, and be costed. In the TRAILBLAZER-ALZ 2 (phase III) trial of donanemab, 1 in 4 of those failing to meet eligibility criteria were excluded due to “low amyloid pathology”. Therefore, a considerable proportion of patients presenting to services with symptoms of memory impairment would be deemed ineligible due to ‘negative’ amyloid results, but potentially eligible in the future as amyloid accumulation becomes increasing prevalent as people age. The regularity of required subsequent checks of amyloid levels is unknown, and due consideration will need to be given to the fact that this could come to represent something akin to a regular screening programme for some patients. Serial amyloid measurements were used to inform cessation of treatment in the trial. In the longer-term, patients would presumably need to be enrolled in long-term follow-up monitoring to determine if/when amyloid levels return to above treatment thresholds and treatment may need to re-commence, if donanemab is approved for use. None of this is supported by direct evidence, and all of this would include significant associated costs to the health system, and implications for patients and their caregivers. Finally, the health system would need develop approaches to identifying, managing and treating the short-term, and (unknown) long-term adverse effects of the treatments such as MRI monitoring for, and treating complications of, the increased rates of brain oedema (ARIA-E), brain haemorrhage (ARIA-H), and brain volume loss seen in the trials. Pre-treatment counselling on the uncertainty of the long-term effects of these side effects will be required for all patients – notably these side effects themselves represent risk factors for dementia, so

	long-term negative effects on cognition and quality of life could feasibly exceed the small cognitive benefits achieved by the drugs in the trials. And some patients will die, perhaps as a direct result of this treatment or during the treatment for other reasons (concomitant use of anticoagulants and thrombolysis have been implicated). Liability for death would be uncertain but if post-approval monitoring revealed more deaths than expected there could be longer-term consequences for the NHS.
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	No, the treatment pathway would be totally distinct from existing treatments. New care pathways would be needed from eligibility ascertainment through to treatment for adverse events occurring as a result of the treatments (as per answer to q9c).
10a. How does healthcare resource use differ between the technology and current care?	As detailed in answer to q9c, even if donanemab were approved for only a small group that closely resemble the trial population (circa 5-8%), the testing to determine eligibility would include a much larger group of people. At present, this would require either PET scans or lumbar puncture to confirm the presence of amyloid pathology. Efforts are underway to try and validate plasma biomarkers, but so far these have been researched in selective research cohorts that are typically younger, with few neuropathologies (except amyloid), few co-morbidities, and minimal socioeconomic or ethnic diversity. Real-world populations seeking help will be older, have mixed pathology, co-morbidities will be prevalent (including conditions like chronic kidney disease which evidence suggests will affect plasma biomarker accuracy, *Stocker et al., 2023. Association of Kidney Function With Development of Alzheimer Disease and Other Dementias and Dementia-Related Blood Biomarkers. JAMA Network Open*) and more diverse. It is likely that the plasma biomarkers will perform less well in this more complex patient group. MRI scans would also be required to confirm the absence of other significant co-neuropathology (e.g. vascular pathology) which were exclusion criteria in the trials. The treatment itself would require regular infusions at specialist centres for a possibly indefinite period (for some patients) and regular MRI monitoring for adverse events. None of these resources are required for current treatment and holistic management of people with dementia, although a small subset of patients with currently undergo a similar set of diagnostics at specialist centres. In addition it would be important to conduct an impact assessment of the necessary diagnostics and monitoring for impact on NHS aspiration to move towards carbon neutral status.
10b. In what clinical setting should the technology be	It is likely that donanemab would need to be administered in specialist clinics with the capability to determine eligibility, provide regular infusions, and monitor and treat adverse effects. This would have significant effects on

used? (For example, primary or secondary care, specialist clinics.)	patients and their carers, who would need to be able to attend these specialist centres every four weeks. These would not necessarily be close to where they live. The healthcare personnel required for the diagnostics, regular infusions, and adverse event monitoring/treatment, will have to be recruited as well as trained in this specific approach, and it is likely this would mainly be from the current workforce pool, inevitably exacerbating shortages in other fields.
10c. What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	Each stage of this treatment pathway would require investment in resources, in training of a multi-disciplinary workforce to counsel patients, in PET and MRI scanning capacity (i.e. machines, tracers, workforce), and facilities and staff for infusion clinics. As detailed above, patient demand for eligibility testing is likely to be broad, even if the eligibility group is tightly defined and few are actually eligible. It is also likely that a monitoring system/registry would need to be established to capture longer-term data on treatment and safety outcomes (though the utility of these would be limited by the lack of a control group).
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Evidence does not support this conclusion. The best available evidence suggests a minimum clinically important difference in MCI of 0.98 for CDR-SB and 1.26 for MMSE; and in mild Alzheimer's disease of 1.63 for CDR-SB, and 2.32 for MMSE. The phase III trial of donanemab (17% MCI, 83% mild AD) reported effects of 0.70 for CDR-SB, and 0.48 for MMSE, relative to placebo. Thus, after 18 months of treatment with donanemab, the treatment effects represented less than half of what is considered clinically meaningful in mild AD on the CDR-SB score, and less than a quarter for MMSE. Moreover, 'functional unblinding' due to common infusion reactions (8.7% of patients in treatment group compared to 0.5% in placebo group), and higher drop-out in the intervention arm (79.7% of placebo group completed treatment vs. 72.3% of donanemab group) may have inflated the detected difference in outcomes, particularly because they are based on interviews with patients and caregivers. This effect size after 18 months is comparable to (CDR-SB) or smaller than (MMSE) the effect of the only currently available drugs, cholinesterase inhibitors/memantine after 6 months of treatment. These drugs have also had the clinical meaningfulness of their effects questioned – the French healthcare system stopped reimbursing them in 2018 (*Walsh et al., 2019. France removes state funding for dementia drugs. The BMJ)*.

	Moreover, there are concerns about translating the *efficacy* results from the trials of amyloid immunotherapy drugs to *effectiveness* for real-world populations. See uploaded evidence from '*Burke et al., 2023. Lecanemab: Looking Before We Leap. Neurology';* and draft under peer review of '*Walsh et al., 2024. Weighing up the new Alzheimer's drugs: clinical, population, and health system perspectives*. The recruitment centres for the donanemab trial took 16 months to recruit an average of 6 patients each. These patients were on average several years younger, had few/no co-neuropathologies (e.g. vascular disease), and had much fewer co-morbidities, than the real-world populations who are clinically diagnosed with Alzheimer's disease. The effect of this mismatch is that real-world populations would be expected to experience considerably less treatment effectiveness even than the limited efficacy seen in the trials (which was already much less than the minimum clinically important difference). For many of the outcomes considered in the final technology appraisal scope there is no current evidence from trial data that confirms any benefit (e.g. ability to remain independent, admission to full time care, mortality).
11a. Do you expect the technology to increase length of life more than current care?	There is no evidence in either direction from the trials to support or refute this. It should be noted that delaying mortality is not necessarily offered as a priority by people living with dementia or their caregivers – quality of life is typically prioritised. Given that more than 1 in 4 patients on donanemab were not able to complete the phase III trial, it is possible that those who are able to complete a course of treatment without dropping out due to side effects or other factors will be those who are more physiologically robust at the outset. If any future evidence does suggest longer life expectancies for those on treatment, care would need to be applied to ensure it is not actually due to this bias.
11b. Do you expect the technology to increase health-related quality of life more than current care?	It is not possible to answer this question directly and with confidence, given the data available. But on balance, it seems unlikely. Quality of life outcomes have not been reported for donanemab. But they have been published for the similar drug, lecanemab (*Cohen et al., 2023. Lecanemab Clarity AD: Quality-of-Life Results from a Randomized, Double-Blind Phase 3 Trial in Early Alzheimer's Disease. JPAD)*. These results show some divergence, but no statistically significant differences between lecanemab and placebo in the EQ-5D-5L at the 6 and 12 month follow-up time points. In the analysis at 18 months, there is a 2/100 point difference (hyperbolically reported in relative rather than absolute terms in the paper) in the average of the two groups, which is statistically significant. The Cohen et al. paper also includes analysis of caregiver's quality of life, using the Zarit Burden Interview.

	These results were statistically significantly in favour of lecanemab at all time points, with an absolute difference at 18 months of around 2 out of 88. Again, partial unblinding due to common infusion reactions in the active treatment arm may have affected the score on these assessment instruments. As stated, these outcomes have not been reported for donanemab, but there are four reasons why it is not possible to infer with confidence whether the statistically significant differences for lecanemab would translate into meaningful improvements in quality of life beyond current care for either drug. (1) As with all outcomes for the amyloid immunotherapy agents, the absolute effect sizes are very small. A difference of 2 out of 100 after 18 months of treatment is simply too small to confidently infer meaningful patient/system benefit in the short- or long-term. (2) As detailed in the response to question 11, the mismatch between trial and real-world populations means that clinical effectiveness is likely to be much reduced (Burke et al., Walsh et al.). (3) The analysis by Cohen et al., includes only those who completed the trial and had reported quality of life outcome data (at 18 months: 79.6% of those randomised to lecanemab, 84.1% of those randomised to placebo), and may therefore represent attrition bias (as those who suffer worse quality of life, worse side effects, or death whilst taking the treatment may/will be more likely to drop out). (4) Quality of life scores, both patient and caregiver, are susceptible to bias if the respondent correctly suspects their treatment arm. Given the frequency of adverse events in the clinical trials, such as 26.4% of lecanemab patients (7.4% placebo) experiencing infusion-related reactions, and 21.5% (9.5% placebo) experiencing ARIA, the possibility of 'functional unblinding' (i.e. patients/caregivers inferring that they are in the treatment arm and this (unconsciously) biasing their reports towards a more positive effect) affecting these results cannot confidently be excluded.
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	As discussed in the uploaded papers from Burke et al. and Walsh et al., and described in the answer to Q11, the trials were conducted in people typically younger, with less co-neuropathologies, and less co-morbidities, than the overall population with Alzheimer's disease seen in memory services, and even more so than those seen in other services such as old age medicine clinics. Treatment in real-world populations could therefore be restricted to those who match the trial population closely, but this would be a very small number of people (on average, recruiting centres for the donanemab trial recruited only 6 patients each during a 16 month window; see also evidence above from Pittock et al.). If treatment were offered more broadly, to those who are either older, have a greater burden of other neuropathologies at diagnosis, and/or those with more co-morbidities, then the treatment response in these more complex and heterogeneous patients would be expected to be smaller than the (already small) effects seen in the trials. It is also likely that the side effects will be more prevalent in real-world

	populations compared to the immunotherapy trial populations (*Burke et al., 2023. Lecanemab - Looking Before We Leap. Neurology*). In both the donanemab and lecanemab trials, subgroup analyses suggested the possibility that results were less good in women compared to men. However, as these were subgroup analyses, and the trial effect sizes so small, it is difficult to conclude anything from this. Indeed the trial authors of the lecanemab trial themselves confirmed that their trial was not powered to identify any between-sex differences in efficacy in their response to correspondence published by the New England Journal (https://www.nejm.org/doi/full/10.1056/NEJMc2301380), and this is also the case for donanemab.

The use of the technology

13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	Donanemab would be much more difficult than existing treatments. Donanemab requires a lumbar puncture or PET scan, as well as an MRI scan and possibly APOE genotyping, to determine eligibility and allow informed consent about risks of treatment. The majority of patients (79% in the phase III trial, likely 92-95% in a population-based sample *Pittock et al.*) and their caregivers will need to deal with the upset of being told they are not eligible. Those eligible must then attend a treatment centre every 4 weeks for a potentially indefinite period, during which they must be well enough, and settled enough, to tolerate an intravenous infusion. They must also undergo repeated MRI scans to monitor for adverse events. Regular infusions and serial MRI scans are clearly not preferable aspects of treatment for a condition in which behavioural symptoms are common. The substantial minority that experience side effects will need further monitoring, with unknown impact on iatrogenic health impacts and quality of life.
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these	Yes, as described in more detail in the answer to q9c, demand for treatment will be broad. Eligibility which matches the trial population will require all of these people to undergo lumbar puncture or PET scanning, and an MRI scan and possibly APOE genotyping, to determine their eligibility and make an informed decision. In the phase III donanemab trial, serial PET scans were undertaken to determine when brain amyloid levels dropped below a set threshold, at which point treatment was stopped. This means at least two amyloid PET scans

include any additional testing?	(to determine eligibility and evaluate therapy effect on this biological parameter). Amyloid "clearance" was achieved by 30% of participants at 6 months and 76% at 18 months. There would then, presumably (no trial evidence to inform the approach), need to be a follow-up programme established to repeat the PET scan at regular intervals to determine when amyloid levels re-exceed thresholds, and eligibility for re-starting treatment be completed (i.e. checking that no excluded co-neuropathologies or co-morbidities had developed in the meantime).
15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	There is no evidence to suggest that the changes seen would translate into any wider benefits. It is important to consider the practical challenges of adhering to this treatment, and relatedly, to include caregiver perspectives in terms of quality of life.
16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	There is no evidence to support this. It is clear that the effect sizes seen in those who completed the 18-month trial period are not enough to produce a "substantial impact" on people living with clinically diagnosed early Alzheimer's disease. It is only possible to argue for meaningful patient benefit from these treatments if one accepts that these drugs are disease-modifying - i.e. that the amyloid cascade hypothesis is correct, that the accumulation of amyloid pathology is the cause of a downstream series of other brain changes which drive the dementia syndrome in these patients, and that these drugs given at this stage of the disease process are sufficient to avoid this cascade. There is no empirical clinical evidence to tell us whether this is the case or not, the underlying biological evidence as to whether the cascade hypothesis is correct or not is incomplete, and indeed the cascade hypothesis is subject to considerable doubts (*Kepp et al., 2023. The amyloid cascade hypothesis: an updated critical review. Brain)*. Unless one accepts the controversial amyloid cascade hypothesis, pretty much in its entirety, then it is very difficult to consider that the likelihood of theoretical disease modification justifies the costs, adverse events, logistical challenges, and opportunity costs of donanemab. It is also important to note that, in the event of approval by NICE and clinical adoption within the NHS, establishing a registry of patients will still not definitely confirm long-term disease modification, because of the inherent lack of a control group.
16a. Is the technology a 'step-change' in the	Given the answer to q16 above, and within the confines of current evidence, no.

management of the condition?	
16b. Does the use of the technology address any particular unmet need of the patient population?	Given the answer to q16 above, and within the confines of current evidence, no. Moreover, the resource implications of rolling out this treatment within the NHS would mean a significant opportunity cost which could worsen the overall experience of people living with dementia and their carers in the UK.
17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	The phase III trial showed that, in keeping with other drugs in this class, donanemab causes significant adverse events. 24.0% (205/853) of participants treated with donanemab developed brain oedema detectable by imaging (placebo group 1.9%), 25% of whom were symptomatic. 19.7% (placebo 7.4%) experienced brain haemorrhage, almost always asymptomatic, though the long term effects are unknown. 13.1% (placebo 4.3%) experienced adverse events severe enough to discontinue the trial. Donanemab was considered related to 3 deaths during the trial (placebo 1 death), and more generally this class of drug has been associated with deaths due to brain haemorrhage associated with receiving amyloid immunotherapy infusions alongside anticoagulants or thrombolysis. This has significant implications for any prospect of broadening eligibility for these drugs beyond the very tight criteria applied in the trials (in which those with any significant co-neuropathology indicating cerebrovascular disease, or any history of TIA or stroke, were excluded), to a real-world clinical population in which stroke and/or bleeding risk is likely to be higher. The potential need for MRI monitoring during treatment to identify ARIA side effects adds to the overall patient/caregiver burden of clinical attendance associated with the treatment.

Sources of evidence

18. Do the clinical trials on the technology reflect current UK clinical practice?	No, as described above. Although a small subset of patients may receive a similar diagnostic work up at specialist centres, there is no treatment in current practice that is remotely similar. The intensity of the treatment, once individuals are identified as sufficiently similar to those who persisted in the trial, approximates that required for some types of cancer treatments, although those tend to be for shorter periods, and have a stronger evidence base.
18a. If not, how could the results be extrapolated to the UK setting?	As described previously, transposing the trial protocols to the UK setting would require major investments across diagnostics, workforce and treatment facilities and the establishment of a whole new pathway. As also noted above, careful consideration must be given to the highly selected nature of the trial population and how few patients would meet inclusion/exclusion criteria – and indeed why the trials were designed to be so selective (to

	maximise the treatment effect, which was still quite small, and to minimise drop out due to the treatment burden and side effect risk).
18b. What, in your view, are the most important outcomes, and were they measured in the trials?	Slowing in the rate of cognitive and functional decline could be an important outcome if it were of a magnitude of clinical relevance, and more importantly, perceived as meaningfully improving (relative to placebo) quality of life by both patients and those around them. In the trials, amongst those who completed 18 months of treatment, the reported slowing of cognitive decline was not close to reaching clinical relevance. Longer-term trial data would be required to support theoretical assertions of disease modification, and to better understand the long-term effects of the increased rates of brain swelling and bleeding observed in the trials. Trials which include processes for monitoring of re-accumulation of amyloid pathology after cessation of treatment are required in order to confidently estimate the overall cost to the system (and the practical implications for patients in order to be able to take informed consent from them to initiate treatment). Data on delayed time to transition from mild to moderate disease, numbers of hospital admissions, time until admission to nursing home facilities etc. would also be of value but do not exist. These important outcomes are reflected in the final scope for this NICE evaluation.
18c. If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	It is not possible to conclude that the treatment effects (i.e. the change in the amount of cognitive decline observed at 18 months amongst completers) are sufficient to support clinical adoption in the NHS. It is only possible to argue this if a theorised disease modification, and therefore cumulative benefit over time, is assumed. Therefore, in submitting this therapy for approval, the manufacturers are effectively using amyloid removal as a surrogate marker for long-term clinically relevant treatment outcomes. It was agreed in 2018 by the European Medicines Agency, of which the MHRA was at the time a member, that amyloid removal was not an acceptable surrogate endpoint for this class of drugs (https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-clinical-investigation-medicines-treatment-alzheimers-disease-revision-2_en.pdf). No substantial change in the evidence base since that time supports the abandonment of that decision. Moreover, there is strong evidence from meta-analysis that amyloid removal results in no, or little, change in cognition (*Richard et al., 2021. Bayes analysis supports null hypothesis of anti-amyloid beta therapy in Alzheimer's disease. Alzheimer's & Dementia*) (*Ackley et al., 2021. Effect of reductions in amyloid levels on cognitive change in randomized trials: instrumental variable meta-analysis. The BMJ) (Ackley et al., 2023. Estimated Effects of Amyloid Reduction on Cognitive Change: A Bayesian Update across a Range of Priors. Alzheimer's & Dementia).*
18d. Are there any adverse effects that were	In the trials of amyloid immunotherapy agents, the number of deaths were small. However, in the open label extension of lecanemab, 3 deaths were reported to be associated with use alongside therapies which inhibit blood

not apparent in clinical trials but have come to light subsequently?	clotting (i.e. anticoagulants and thrombolysis). Given the high-rate of brain haemorrhage in the treatment arm of the trials, the notion that amyloid immunotherapy with concomitant use of anticoagulants or thrombolysis could increase the risk of fatal bleeding is biologically plausible and very concerning. Moreover, the donanemab trial population was carefully selected to exclude participants who had a history of TIA or stroke, significant medical co-morbidity, or MRI evidence of cerebrovascular disease. Logically, any clinical use of donanemab in a patient cohort that is more reflective of the real-world population with Alzheimer's disease would be expected to be associated with an increase in these events.
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	The uploaded evidence from *Walsh et al.,* is currently under peer review and may or may not be published at the time of a NICE evidence review. It outlines the mismatch between the clinical trial cohort and the real-world population with early Alzheimer's disease, and considers the significance of this mismatch for drug approval, regulation, and clinical adoption. It will be relevant for the evaluators to be aware of efforts to change the definition of 'Alzheimer's disease' over recent years. Historically, the label of Alzheimer's disease was confined to those who have clinical dementia (cognitive decline leading to functional impairment) which is attributed to amyloid- and tau-based neuropathology. More recently, and closely linked to endeavours to bring drugs and biomarkers to market, some have argued for Alzheimer's disease to encompass anyone with evidence of beta-amyloid plaque accumulation, irrespective of symptoms. Indeed, the reference to 'early symptomatic Alzheimer's disease' in the phase III trial of donanemab, whilst including those with mild cognitive impairment (i.e. not meeting dementia syndrome criteria) but with amyloid positivity is an example of this 'disease creep'. The relevance of this is that amyloid positivity, even in the presence of mild cognitive impairment, does not guarantee lifetime occurrence of dementia – particularly at older ages (*Brookmeyer, 2018. Estimation of lifetime risks of Alzheimer's disease dementia using biomarkers for preclinical disease. Alzheimer's & Dementia)*. This becomes highly relevant when considering the minimal treatment effects, high side effects, intense treatment requirements, and high costs associated with donanemab. Further, population evidence shows that the 'pure' Alzheimer's seen in the trial cohorts (i.e. amyloid and tau positivity but minimal other neuropathologies such as vascular pathology or other proteiniopathies) is rare, particularly at older ages. Indeed, Alzheimer's type pathology (cortical neuritic plaques and neurofibrillary tangles) was shown to be associated with only 20% of 'usual' dementia at death in epidemiological neuropathology studies (*Matthews et al., 2009. Epidemiological Pathology of Dementia: Attributable-Risks at Death in the MRC Cognitive Function and Ageing Study. PLOS Medicine*) (*Schneider et al., 2007. Mixed brain pathologies account for most dementia cases in community-dwelling older persons. Neurology) (Wharton et al. 2023. Insights into the*

	pathological basis of dementia from population-based neuropathology studies. Neuropathology and Applied Neurobiology).
20. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance TA217	
21. How do data on real-world experience compare with the trial data?	The uploaded pre-publication draft from '*Walsh et al.,* outlines the mismatch between the clinical trial cohort and the real-world population with early Alzheimer's disease. On average, the phase III trial recruiting centres enrolled 6 participants each over a 16 month recruitment period, and the trial exclusion rate was 79% (i.e. for every 10 people tested for eligibility, 8 were deemed ineligible – the effect this rejection has on patients and their caregivers is an externality of any analyses of donanemab on patient outcomes, but should not be ignored), indicating the highly-selective nature of these trials. The analysis from Pittock et al. in a population-base sample suggests 8% of patients seeking treatment in real-world settings would meet trial eligibility criteria. Broadening eligibility criteria to increase access to the drugs would be expected to lead to smaller treatment effects, and higher rates of adverse events.

Equality

22a. Are there any potential equality issues that should be taken into account when considering this treatment?	Any treatment pathway that is difficult to access, navigate, or complete will drive health inequalities as those with more agency and resources will find it easier to 'adhere' (assuming there is a positive impact). In donanemab's case, the hypothetical pathway would tick each of these boxes, primarily driven by the need to attend infusion centres regularly, and the number of eligibility and monitoring tests required. It is important to note that an inequality in access to a non-clinically meaningful treatment cannot, by definition, lead directly to an exacerbation in health inequalities (because the treatment does not deliver any actual health benefit). But the feeling of missing out on a 'wonder drug' (as per the media hype) will drive a perception of relative disadvantage amongst those deemed ineligible or for whom undertaking the treatment regimen is not feasible (e.g. because of travel distances or lack of reliable transport options). The opportunity cost created by the drugs would also increase health inequalities, as services under existing strain would be massively distracted by attempting to deliver this treatment. As services decline the effect is always seen more profoundly for those from more deprived socioeconomic circumstances.
22b. Consider whether these issues are different from issues with current care and why.	As the whole treatment pathway would be new, all of the described equality issues would be caused by donanemab's approval.

Key messages

23. In up to 5 bullet points, please summarise the key messages of your submission.	• Evidence does not support that donanemab produces a clinically meaningful benefit in cognition and function, and there is a lack of evidence on this and other outcomes of relevance due to the trial's 18-months duration, and no evidence on any effect beyond that. • Clinical relevance could therefore only be achieved via a theorised disease modification, but there is insufficient evidence to support this, and using amyloid removal as a surrogate endpoint is explicitly contrary to guidance. • Therefore, it is not possible to conclude that the treatment effects justify the very high costs, adverse events, practical implications for patients, caregivers, clinicians, and the health system, and opportunity costs. • The trial cohort is highly unrepresentative of those with clinically diagnosed Alzheimer's disease in clinical practice. Few in NHS clinics would satisfy the full eligibility criteria of the clinical trials, and the disappointment of being 'rejected' for treatment (i.e. ineligible) is an important externality. • Any broadening of the eligibility criteria would be expected to lead to diminished (already non-clinically meaningful) treatment effects, and increased likelihood of adverse events.

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NICE National Institute for Health and Care Excellence

Single Technology Appraisal

NICE appraisal invitation - consultees: Alzheimer's disease (mild cognitive impairment, mild dementia) - donanemab [ID6222]

Professional organisation submission

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 13 pages.

NICE National Institute for Health and Care Excellence

1. Your name	[redacted]
2. Name of organisation	Faculty of Old Age Psychiatry, Royal College of Psychiatrists
3. Job title or position	All contributors are Consultant Old Age Psychiatrists working in the NHS. [redacted]
4. Are you (please select Yes or No):	An employee or representative of a healthcare professional organisation that represents clinicians? **Yes** ~~or No~~ A specialist in the treatment of people with this condition? **Yes** ~~or No~~ A specialist in the clinical evidence base for this condition or technology? **Yes** ~~or No~~ Other (please specify): These replies are relevant to all individuals listed as above
5a. Brief description of the organisation (including who funds it).	The Royal College of Psychiatrists (RCPsych) is the professional medical body responsible for supporting psychiatrists throughout their careers from training through to retirement, and in setting and raising standards of psychiatry in the United Kingdom. The RCPsych has charitable status and is mainly funded by member subscriptions. The Faculty of Old Age Psychiatry (Old age psychiatry faculty | Royal College of Psychiatrists (rcpsych.ac.uk)) within the RCPsych represents psychiatrists across the devolved nations who work at the forefront of dementia diagnostic and treatment NHS services. Through an extensive network of memory clinics and related services, we assess and support most patients with early Alzheimer's disease via the NHS and hope our expertise and insights will be relevant to this guidance. Old Age Psychiatry services have been established in the NHS from the 1970s and represent the largest service providing expertise in the diagnosis, treatment and care of people with dementia. A recent example of our work in this area is a joint project with ARUK to explore our readiness to deliver new modifying treatments: Are we ready to deliver disease modifying treatments? | Royal College of Psychiatrists (rcpsych.ac.uk)
5b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months?	No - the Faculty has not received any funding
5c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No - the Faculty has not received any funding from the tobacco industry

The aim of treatment for this condition

6. What is the main aim of treatment? (For	To delay the clinical and biological progression of Alzheimer's disease (AD) and thereby reduce the overall impact of the illness. Thinking of AD progressing through various stages – the aim would be to slow progression to more advanced clinical stages - such as delaying progress from 'prodromal-

example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	MCI AD' and/or 'mild dementia' to 'moderate' and 'severe' stages of dementia (e.g. using the global CDR score used in clinical trials, this would be progressing from 0.5 [MCI] to 1[mild AD dementia] or 1 [mild dementia] to 2 [moderate dementia]) Delaying the progression carries the hope there will be favourable outcomes with respect to reduced symptoms, improved functioning, well-being and quality of life, reduced care needs and family stress, reduced health and social care costs, and delayed mortality. Because AD has such a high prevalence, long duration and high levels of morbidity and mortality, it has been estimated that a relatively small difference in slowing the course of the illness could have a significant overall impact on the disease burden. For example, Lewis et al (from 2014 - *Trajectory of Dementia in the UK – Making a Difference, report produced the Office of Health Economics for Alzheimer's Research UK*) estimated that: (though this report does not include the drug and treatment related costs of monoclonal antibody therapies) • If the onset of dementia could be delayed by 2 years, there would be 19% (383,000) fewer people with dementia and 325,000 fewer informal carers, thus the cost to the economy would be 22% less (saving £12.9bn) in 2050. • If the onset of dementia could be delayed by 5 years, there would be 666,000 fewer people with dementia and 566,000 fewer informal carers, thus the cost to the economy would be 36% less, saving £21.2 billion in 2050. • If from 2020 a new treatment could slow the progression of dementia by 25%, by 2050 there would be 6% fewer people living in the severe stages.
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	By way of background context to this question: a. AD is a progressive brain disease, and the underlying pathology is estimated to start at least 10-15 years before symptom onset. It is also a complex disease with multiple putative molecular mechanisms at play, and our understanding of its pathogenesis remains incomplete. Clinical progression and impact are variable between people and over time, and progression is likely to be affected by many variables including genotype, medical co-morbidities, age, gender, lifestyle, social and environmental factors. An added complication is that often (in an estimated 70% of cases) people with AD will also have other pathological changes that could directly or indirectly also be contributing to their clinical presentation. Therefore, given our current state of knowledge and influence over the pathology, it seems reasonable to impute advances in therapeutics which target specific aspects of AD may, realistically, yield modest clinical benefits reflected in the slowing of the disease process rather than stabilising or reversing the disease. In the future it seems reasonable to expect combination therapies will be required (as – by analogy- have all complex diseases across medicine as a whole – indeed as already see in the combination of cholinesterase inhibitors (CHI) with memantine). b. It should be acknowledged there is no established consensus about which outcome measures provides the "best" answer to this question. Guidance from regulators (for example FDA and EMA) have preferred clinical outcome measures for dementia trials that are a composite measure of cognitive and functioning evaluated by an experienced clinician blind to other aspects of the study (e.g. such as the CDR as discussed further below). However, in the broadest terms opinions vary from the notion of using a single critical predetermined outcome measure – such as the construct of a "minimal clinical meaningful difference" (MCID) (Andrews et al. Alzheimers Dement (N Y) 2019 Aug 2;5:354-363; Liu KY et al, Lancet Psychiatry. 2021 Nov;8(11):1013-1016) to one that posits a broader framework is required that examines this question from a number of perspectives – as illustrated in the table below from reference "Meaningful benefits: a framework to assess disease-modifying therapies in preclinical and early Alzheimer's disease" from Alzheimers Res Ther. 2022; 14: 54.). This viewpoint often emphasizes Alzheimer's disease does not progress in a linear fashion and in the earlier phases of the illness (such as prodromal AD) clinical changes (especially over the timeframe of 18-month clinical trial) may be less evident than at later stages of the illness. Further, existing rating scales can vary in their ability to detect this early change (having been mainly developed and validated in more advanced stages of the illness, sometimes many years ago (eg MMSE = 1975, CDR dates = 1982). We have seen more recent clinical trials developing different rating scales to try and address this issue: for example for donanemab – the integrated Alzheimer Disease Rating Scale (iADRS) was used as the primary outcome measure. The iADRS is an integrated assessment of cognition and daily function from the 13-item

cognitive subscale of the Alzheimer Disease Assessment Scale (ADAS-Cog13) and Alzheimer Disease Cooperative Study—Instrumental Activities of Daily Living (ADCS-iADL) though these new scales are not yet well established in clinical practice so it can be difficult to infer / interpret the numerical relevance of differences). Overall, trends in defining clinical benefit of disease modifying treatments (DMTs) in AD recognise there are different ways to answer this question, with different measures and forms of analysis potentially being preferred by regulators, clinicians, patients, carers and funders respectively (eg A systematic review: International Consortium Real World Outcomes Across the AD Spectrum for Better Care (ROADMAP) - Alzheimers Dement (Amst). 2019 Dec; 11: 231–247). Related challenges about interpreting clinical outcomes are debated by Liu KY et al Brain Commun 2023 Jun 2;5(3) and Liu et al, Lancet Healthy Longev 2023;4: e645–51.

a. **Clinical Trial Outcomes**	a. **Measures**	b. **Emerging / Novel Measures**
c. **Conventional outcome measures** - Cognition - Function - Behavioural - Neuropsychiatric - Global d. **Patient-reported outcomes (PROs)** - minimal important difference (MID) e. **Care partner reported outcomes** - quality life / stress - burden f. **Socioeconomic variables** g. - resource utilization	h. **Effect size (Cohen's D, SRM)** i. **Risk ratio / odds ratio** j. **Numbers need to treat** k. **Numbers need to harm** l. **Time to event** m. **Meaningful change and difference** thresholds – minimal clinical meaningful difference (MCID)	n. **Cumulative benefit:** o. Increasing drug-placebo difference over time p. **Predictive benefit:** q. Biomarker-based prediction of outcome r. **Progression time saved/gained**

A further factor we think is relevant in answering this question relates to extent of clinical change observed in the placebo group in the donanemab trial. This gives an indication of the amount of change that occurs in individuals selected using the same eligibility criteria as those participants on active medication. So for example – looking at the data for the Clinical Dementia Rating Sum of Boxes (CDR-SB) – the placebo group declined by between 1.84 to 2.42 least square means (depending on baseline tau group) points on this 18 point scale over 18 months (compared to 1.16 to 1.72 in the donanemab group).[The least-squares mean change in CDR-SB score at 76 weeks was 1.20 (95% CI, 1.00-1.41) with donanemab and 1.88 (95% CI, 1.68-2.08) with placebo (difference, −0.67 [95% CI, −0.95 to −0.40]; $P < .001$) in the low/medium tau population and 1.72 (95% CI, 1.53-1.91) with donanemab and 2.42 (95% CI, 2.24-2.60) with placebo (difference, −0.7 [95% CI, −0.95 to −0.45]; $P < .001$) in the combined population].

Finally – it is important to note that CHI are prescribed for the dementia stages of AD – so for the donanemab study approximately 56-61% of participants were were also receiving approved treatments for AD (with approximately 80-84% diagnosed with mild Alzheimer's dementia). A further debate in the literature has centred on how the effect size seen in clinical trials with DMTs like donanemab compares to established treatments using CHEI and memantine. There have been no head-to-head studies between CHEI and monoclonal antibody therapies and emerging trends in trial design over the past 20 years can make direct comparisons difficult: eg different use of biomarkers, diagnostic and eligibility criteria, stage of illness, statistical approaches, trial duration, and rating scales.

	Taking these issues and findings into consideration – when answering this question, we are of the opinion that clinically meaningful benefit would be supported by: a. **Using multiple outcome measures**: observing statistical differences across all primary and secondary outcome measures as together this consistency of effect from different perspectives would strengthen the view a drug is likely to be clinically beneficial. b. **Focusing on iADRS as the primary outcome measure,** this composite measure clinically evaluates both cognition and function involving both and we are of the opinion that a difference in change of > 30% slowing on this scale over 18 months represents a meaningful though modest clinical benefit. (With the caveats mentioned previously about relying on a single measure, this difference would be consistent with Vellas B et al European Task Force group. Disease-modifying trials in Alzheimer's disease: a European task force consensus. *Lancet Neurol*. 2007;6(1):56-62; Insel PS et al Determining clinically meaningful decline in preclinical Alzheimer disease. *Neurology*. 2019;93 (4):e322-e333). c. Though opinions vary about the utility and validity of this measure*, converting the **difference in IADRS and CDR-SB over time into a proxy measure for "time saved"** can offer a novel and intuitive way of describing whether or not a drug is likely to be clinically beneficial. We think a difference of around 4-6 months represents a modest clinically meaningful benefit that patients' would find helpful when considering whether (or not) this treatment is right for them. We think this notion of "time saved" offers parity of effect with other drugs that are licenced for different types of cancer (*eg Goldberg TE, et al. J Neurol Neurosurg Psychiatry 2023;0:1–6., argue for a greater use of effect sizes and NNTs, rather than relative per cent slowing, d. **Using global CDR scores** – to demonstrate slowing in the progression from one stage of AD to the next.
8. In your view, is there an unmet need for patients and healthcare professionals?	Definitely. Alzheimer's disease is the main cause of dementia accounting for approximately 60% of cases, and overall dementia is the leading cause of death in the UK. (Office for National Statistics). As described in the next section – there are no DMTs for AD and no biological treatments for the earlier stages of the illness before the onset of dementia. It would be logical to impute that disease modifying treatments are likely to have their greatest long-term impact and benefit the earlier they are used.

What is the expected place of the technology in current practice?

9. How is the condition currently treated in the NHS?	For patients with prodromal-MCI AD, there are no biological treatments available (symptomatic or disease modifying). In the absence of a treatment, people diagnosed in the NHS with prodromal – MCI AD are usually discharged from memory clinics back to primary care, with the advice to be re-referred if their symptoms progress (which for a patient with underlying AD is inevitable). For patients with AD dementia (mild, moderate, and severe) there are recognised treatments (cholinesterase inhibitors and memantine) as approved by NICE (but not MCI-AD). However, these treatments are considered symptomatic interventions of modest effect size and do not slow or delay the illness Management is, of course, broader than medication and covers a range of biopsychosocial interventions over the course of the illness. [As discussed

	later, most if not all Old Age Psychiatry services across the NHS have no or very limited access to diagnostic biomarkers that can help detect the pathological changes associated with the illness. This applies to all stages of the illness and is particularly evident in relation to the lack of molecular biomarkers, either via PET imaging or CSF biomarkers. This lack of existing infrastructure is also highly relevant should use of donanemab require biomarker determination prior to treatment to assess treatment eligibility. Limited access to MRIs is also anticipated – multiple MRIs are likely to be required initially to establish eligibility (eg to establish how much vascular disease is present) and then used for safety monitoring of amyloid-related imagining abnormalities (ARIA)].
9a. Are any clinical guidelines used in the treatment of the condition, and if so, which?	For patients with AD dementia (mild, moderate, and severe) there are recognised treatments (cholinesterase inhibitors and memantine) as approved by NICE (NG97 2018). In the USA "Appropriate Use Recommendations" (AUR) for lecanemab have been published (Cummings, J.et al Lecanemab: Appropriate Use Recommendations. *J Prev Alzheimers Dis* **10**, 362–377 (2023). https://doi.org/10.14283/jpad.2023.30). Both the AUR and FDA product labelling for lecanemab stipulate testing for ApoE ε4 status should be performed prior to initiation of treatment to inform the risk of developing ARIA, raising the attendant need for genetic counselling. Compared to the FDA, the AUR adopts a more cautious approach by recommending patients receiving anticoagulants are not treated with lecanemab and receive an additional planned MRI at one year. If donanemab is approved, it is our opinion adopting a similar framework as referenced in AUR criteria for lecanemab to donanemab (adapted to the UK setting) would represent the best way forward when initially using this medication. It would mean the drug would be used in a targeted way that matches the eligibility criteria for the phase III study. This could be viewed as a measured and targeted way to balance the benefits vs risks of using donanemab whilst also acknowledging the logistical challenges ahead delivering this treatment in the current NHS. Until further evidence is available, it is reasonable to assume concerns about safety will be greater in real-world populations compared with trial populations and starting with a cautious approach will also offer clarity to inform patient choice.
9b. Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	There are very well-established Old Age Psychiatry services in the NHS that provide the backbone for the assessment and management of patients with AD, predominantly those with dementia due to AD. Indeed, these services are rarely commissioned to provide access to imaging and molecular biomarkers (even though endorsed by NICE in 2018) and currently they do not deliver any monoclonal antibody therapies. In addition, there a small number of neurological and geriatric medicine services that offer cognitive assessments. Memory clinics are primarily located in Mental Health Trusts in England, and greater integration between Acute (Neurology/Neuroradiology, Medical Physics) and Mental Health Trusts (Old Age Psychiatry) would be required to deliver donanemab. [Via a national survey of Old Age Psychiatrists conducted in 2020 in collaboration with ARUK (Are we ready to deliver disease modifying treatments? | Royal College of Psychiatrists (rcpsych.ac.uk)), we know that colleagues across the four nations see the introduction of a DMT as a very important step forward in the management of AD and they are keen to explore how to deliver this treatment holistically within clinical practice. That said various challenges delivering DMTs were highlighted including: Access to, and use, of biomarkers / Concerns about diagnostic accuracy of prodromal AD / Variations in diagnostic terminology – current there are at least 6 different diagnostic terms to describe the population of people who are likely to be developing AD but do not yet have dementia / Lack of readiness of services to meet the challenges of delivering DMT with to staff training and expertise, limited capacity and infrastructure, costs, and lack of commissioned care pathways. Therefore, further consideration will be required as to what constitutes the best care pathways to ensure how donanemab can be safely, effectively and equitably prescribed]

9c. What impact would the technology have on the current pathway of care?	If approved, a DMT like donanemab could represent a shift in the approach to diagnosing and managing dementia as a whole. It could offer greater hope and a better future for patients, reduced future costs and lowering the morbidity associated with the illness. It could help to reduce stigma, encourage greater access to support and advice. However, depending on the regulatory approval for the drug and outcome of NICE appraisal, it could create significant additional demands across both primary and secondary care, especially for prodromal AD as there is no existing treatment pathway for this stage of the illness. This would require new care pathways to be established. It is difficult to estimate the size of the demand for this treatment. For example: • RAND report: (*Hlavka, JP, et al How Prepared Are European Health Care Systems to Deliver a Future Alzheimer's Treatment? An Assessment of Health Care Infrastructure in France, Germany, Italy, Spain, Sweden, and The United Kingdom. Santa Monica, CA: RAND Corporation, 2018. https://www.rand.org/pubs/infographics/IG143.html.)* estimates in the UK that from the pool of 2.3 million people who could be eligible for a DMT by virtue of a diagnosis of prodromal AD or MCI around 0.4 million could be eligible for infusion therapy with a DMT. • The Alzheimer's Society estimate at least 106,000 people could benefit from mAbs if available in the UK. (Alzheimer's Society: https://www.theguardian.com/society/2022/nov/30/nhs-nowhere-near-ready-to-deliver-alzheimers-drug-lecanemab-doctors-say) • Under current service arrangements, Alzheimer's Research UK estimates that only 2% of patients eligible for mAbs would have access to this treatment (ARUK: https://www.alzheimersresearchuk.org/full-lecanemab-data-presented-at-ctad-alzheimers-congress/) • If the AUR criteria as described above are applied – then we anticipate this would focus the use of lecanemab to selective number of people with early AD. For example, estimates for the use of a different monoclonal antibodies - aduacanumab in the USA (*JAMA, September 9, 2021.doi:10 1001/jama.2021.15286*) suggested between 85% and 92% of patients with MCI or AD would not meet the eligibility criteria when matched with the criteria used in the RCTs. In the UK, Laurell A et al (2023 - Estimating Demand for Potential Disease modifying Therapies for Alzheimer's Disease in the UK | medRxiv) estimated approximately 30,000 people with Alzheimer's disease would be eligible to receive donanemab and lecanemab using the inclusion criteria from the clinical trials (with consideration given to diagnosis, cognitive performance, cerebrovascular disease, and willingness to receive treatment) There are concerns that NHS services will not have sufficient capacity (infrastructure, workforce and access to diagnostic technology) to deliver this treatment, and this could lead to longer waiting times generally. This will be a critical issue as if these drugs are most effective when administered early in the symptomatic stages of the illness – delays in diagnosing new patients coupled with existing long waiting lists for current patients, could lead to a situation where delays prevent timely access. An added consideration relates to uncertainties about how long the drug should be administered. Currently patients with prodromal AD or mild AD (once established on treatment and stable) are commonly discharged from secondary care to primary care. However, depending on regulatory approval, it is likely patients on treatment would require long term engagement with services and there is likely to be an increase demand for early assessment and treatment with the risk this could exceed current capacity and lead to longer delays in diagnosis and treatment.
10. Will the technology be used (or is it already used) in the same way as current	We believe it would not be possible to offer donanemab within existing services as "business as usual". We are of the opinion that access to donanemab (and any other future approved monoclonal antibody) would be best overseen by diagnostic and treatment hubs, as suggested below, with the necessary level of expertise, resources, and infrastructure. These hubs would provide the necessary pathways and facilities to diagnose and deliver the treatment for a designated geographical area. In this model, potentially suitable patients would be referred to the hub following an assessment from local secondary care memory services (such as old age psychiatry and medicine and neurology services - having originally been referred to these clinics by primary care). Clear guidance on referral criteria and pathways will be required.

care in NHS clinical practice?	Each hub will require a dedicated leadership team to provide oversight to develop a pathway that integrates the required expertise and services and works with the relevant commissioning body to understand likely demand and develop the necessary capacity to start delivering DMTs. Key limiting factors will be access to biomarker profiling for drug eligibility and MRI to screen for contraindications and risks prior to treatment followed by safety monitoring for ARIA. (Potentially this could mean at least four MRI scans / patient during the first year). Each hub will need to bring together the right skill mix and expertise. Key services to consider integrating will include psychiatry, neurology, geriatric medicine, imaging, medical physics, genetics, pharmacy, informatics, and administration. Key activities within each hub will include: establishing clear consent processes supported by portfolio of patient information materials; implementing the necessary diagnostic and eligibility criteria; providing access to and interpretation of the necessary molecular (PET or CSF) biomarkers and MRI (including optimising access and determining best imaging sequences); ApoE genotyping and counselling; and setting up intravenous facilities and protocols for managing safety and adverse events including infusion reactions and ARIA, including out of hours. Realistically CSF biomarkers would be far more scalable and cheaper than PET and indeed can provide measurements for a broader range of biomarkers. There will be a need to develop a clear process around how therapeutic decision-making using biomarkers will be embedded into clinical practice. Indeed, even within highly specialised memory clinic services, employing amyloid, tau and neurodegeneration biomarkers into real-life settings can be challenging and may yield different patient profiles than seen in research settings. Service protocols would be required to manage the interface between hubs and local services to ensure fair, equitable and timely access that avoids overly complex solutions that disadvantage people. Given the potential duration of treatment, close liaison between hubs and local services will be required to ensure clarity of roles and responsibilities. Support for patients receiving regular infusions over an extended period will be essential, including feasibility of offering home based treatment. The hubs can promote staff training and upskilling as well as opportunities to develop nurse specialist and physician associate roles. Further information about this topic can found: 1.Delivering disease modifying treatments in Alzheimer's disease—An old age psychiatry UK perspective - Int J Geriatr Psychiatry. 2023 Dec;38(12):e6030. doi: 10.1002/gps.6030. 2. Estimating demand for potential disease-modifying therapies for Alzheimer's disease in UK: DOI:10.1192/bjp.2023.166
10a. How does healthcare resource use differ between the technology and current care?	Reply is largely detailed in previous section. Naturally there will be a need to factor in the costs of diagnosis assessmrnt and drug delivery.

10b. In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	This is detailed in Q10 as above. Important questions remain about how to optimise and tailor their use in clinical practice. This includes how to identify those patients likely to benefit; how to treat and monitor response using biomarker and clinical outcomes; understanding subgroup differences; the role of ApoE genotyping and counselling; developing shared-decision approaches; implementing algorithms for managing ARIA and risk mitigation strategies including impact of medical comorbidities and concomitant medications; and the relevance of anti-drug antibodies. Further, key questions remain about the long-term outcomes of using monoclonal antibodies, how long to offer treatment, how much amyloid reduction is required and over what timeframe to be effective, and relationship between non-amyloid biomarker changes and clinical outcomes. Long term outcomes including cost effectiveness, health economic outcomes, quality of life, impact on care and carers and overall mortality are needed. Given the methodological approach taken in the donanemab phase III study to stratify participants by their baseline tau levels, there is a need to evaluate how this factor is taken into consideration in clinical practice? Eg are the results are independent of baseline tau levels or this does influence the clinical outcomes and therefore cost effectiveness?
10c. What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	This could be significant for reasons noted in the other sections.
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	A dilemma comparing the benefits of donanemab with current practice is that for patients with MCI-AD there are no existing treatments nor any head-to-head trials. Furtherstill it should be acknowledged there is a diversity of opinion relating to this matter from across the clinical community with no established consensus view. However – using the criteria we set out in section 7 we are of the opinion that: a. Using multiple outcome measures: observing statistical differences across a range primary and secondary clinical and biological outcome measures demonstrates a consistency of effect It is our understanding that donanemab was demonstrate this pattern of benefit in this patient population. The study reported that of the 24 gated outcomes (primary, secondary and exploratory) 23 were statistically significant. There was a time dependent reduction on PET amyloid equivalent to around reduction in 87 centiloids and to a lesser degree a reduction glial fibrillary acidic protein; but no clear evidence however of a change in PET Tau or Csf neurofilament light chain levels. b. Focusing on the primary outcome measure, the iADRS composite measure clinically evaluates both cognition and function and we are of the opinion that a difference in change of > 30% on this scale over 18 months represents a meaningful though clearly modest clinical benefit. This was achieved in the phase III study - though results varied depending on the level of baseline tau: eg for the iADRS there was a 35.1% slowing (95% CI, 19.90%-50.23%) of clinical progression in the low/medium Tau group compared with 22.3% slowing (95% CI, 11.38%-33.15%) in the combined Tau group.

	Similarly, for the CDR-SB there was 36.0% slowing (95% CI, 20.76%-51.15%) of clinical progression in the low/medium c/w a decline of 28.9% slowing (95% CI, 18.41%-39.44%) in the combined Tau group. c. We also think the conversion of the difference in the key clinical measures (iADRS and CDR-SB) between donanemab and placebo groups into a proxy measure for "time saved" offers a potentially intuitive way of describing whether or not a drug is likely to be clinically beneficial. Overall this equated to approximately 4.4 to 7.5 months "saved" over the 18- month study (low/medium tau population). d. Using global CDR scores – to slow the progression from one stage of AD to the next: participants on donanemab had a 38.6% lower risk of disease progression.
11a. Do you expect the technology to increase length of life more than current care?	If proven this could be a major advantage as AD is a leading cause of death in the UK. However currently there is very limited data about whether donanemab has longer term cumulative benefits after 18 months including prolonging life - this type of data would be key to determining whether any differences observed during the timeframe of a trial disappears, remains stable, or continues to grow over the time (when c/w placebo).
11b. Do you expect the technology to increase health-related quality of life more than current care?	Used selectively in a targeted way this could offer advantages as AD is associated with such significant detrimental personal, family, societal and health costs.
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Available evidence is limited to people with prodromal AD or mild AD. There are no efficacy or safety data for other stages of the disease, or other diseases associated with abnormalities of amyloid homeostasis. Important safety concerns included an increase in amyloid-related imaging abnormalities (ARIA) and ApoE ε4 genotype clearly increased the risk of overall ARIA in a dose dependant way (and ApoE ε4 homozygosity has been proposed as a limit on the use of lecanemab by the US Department of Veterans Affairs). We would anticipate suitable patients would need careful selection covering a range of required eligibility criteria including amyloid positivity, absence of significant medical and vascular comorbidities (confirmed by baseline MRI prior to treatment, exclusion based on certain concomitant medications such as anticoagulants). Patients would require information regarding the risks and potential benefits of the medication, how risk mitigation would be approached, and we would expect all patients to give informed consent (reconciling that patient's should have mild cognitive impairment and that they will need to be able to understand the balance of risks, limitations and benefits of the proposed treatment, including the prolonged and involved nature of the treatment)

13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care?	Donanemab would be more difficult to use – for reasons outlined in previous sections. [Monoclonal antibody treatments are well established in other clinical services across the NHS and Old Age Psychiatry services should be able to "learn" from these services about how best to deliver these treatments
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	**Start criterion:** as described, we would support the adoption of using criteria similar to the AUR for lecanemab (as described by Cummings et al). **Stop Criterion:** We anticipate stop criteria will be determined in two main scenarios: **Adverse events:** Safety monitoring will be a key factor and there will need to be a clear algorithm for managing ARIA. For example the current FDA criteria https://www.leqembi.com/-/media/Files/Leqembi/Prescribing-Information.pdf based on the clinical and radiological severity of ARIA. Infusion reactions – especially anaphylaxis will be important determinates too. **Judging when treatment can be finished?** The evidence base to decide how long to treat remains incomplete. This creates a dilemma about judging whether reaching the amyloid negative threshold represents an outcome that should lead to the cessation of medication or on-going "maintenance" treatment will be required. In the context of this current lack of evidence, coupled with factors such the drug costs, logistics of administration, risks vs benefit and limitations in services capacity – we are of the opinion that the is merit considering whether a course of treatment should last up to 18 months - potentially on the assumption that having reached amyloid "remission" there is little to be gained from further treatment – or conversely if a person fails to convert ("non-responder") then is there value to continuing? Evidence to support prescribing a time limited course of donanemab comes from design of the phase III donanemab study where treatment was stopped when the following PET amyloid criteria were met: If amyloid plaque level (assessed at 24 weeks and 52 weeks) was less than 11 Centiloids on any single PET scan or less than 25 but greater than or equal to 11 Centiloids on 2 consecutive PET scans donanemab was switched to placebo in a blinded (with mean time of 47 weeks over 18 months). Despite stopping treatment the study reported participants continued to show benefits c/w placebo at 18 months (eg CDR-SB difference of 0.75). It may also be relevant and offer cost and logistical benefits to debate whether re-testing a person's amyloid status after a "course" of treatment is clinically beneficial? In the future – blood-based biomarkers may offer much cheaper, more accessible, and less intrusive way to measure molecular outcomes.
15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in	Possibly,

the quality-adjusted life year (QALY) calculation?	
16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	Yes – it has the potential to make a significant and substantial impact on health-related benefits, but as mentioned we need to better understand whether the treatment offers any long-term benefits?
16a. Is the technology a 'step-change' in the management of the condition?	Yes – it has the potential to make a significant and substantial impact on health-related benefits for reasons outlined previously
16b. Does the use of the technology address any particular unmet need of the patient population?	Yes – there is no disease modifying treatment for AD
17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	As previously discussed, a crucial aspect of prescribing donanemab will be to optimise its safe use. ARIA and infusion reactions are clear adverse events that require careful consideration and monitoring. ARIA of oedema/ effusion or microhaemorrhages and hemosiderin deposits occurred in 36.8% of participants receiving donanemab and 14.9% receiving placebo. ARIA oedema/effusion, determined occurred in 24.0% participant in the donanemab group and in 2.1% in the placebo group. A crucial finding from the phase III study was that 3 deaths in the donanemab group and 1 in the placebo group were considered treatment related. This raises significant concerns about using this medication in real-world setting – and adds weight to the opinion that it should be used in a selective, targeted way that aligns closely with the inclusion/exclusion criteria used in the phase III stud (eg similar to the AUR framework advocated for lecanemab) until further safety data available. Additional safety concerns focus on the interaction with other comorbidities and concomitant medications (especially cerebrovascular disease, cerebral amyloid angiopathy, inflammatory vasculitis, and use of anticoagulants) and their longer-term impact on brain health including measures of cerebral atrophy. Questions remain about how to optimise and tailor their use in clinical practice. This includes how to identify those patients likely to benefit; how to treat and monitor response using biomarker and clinical outcomes; understanding subgroup differences; the role of ApoE genotyping and counselling; developing shared-decision approaches; implementing algorithms for managing ARIA and risk mitigation strategies including impact of medical comorbidities and concomitant medications; and the relevance of anti-drug antibodies.

	Further, key questions remain about the long-term outcomes of using mAbs, how long to offer treatment, how much amyloid reduction is required and over what timeframe to be effective, and relationship between tau levels at baseline and other non-amyloid biomarker changes on clinical outcomes. Long term outcomes including cost effectiveness, health economic outcomes, quality of life, impact on care and carers and overall mortality are needed. To determine the most appropriate duration of treatment of a DMT, it will be important to evaluate their cumulative long-term impact beyond the length of a clinical trial.

Sources of evidence

18. Do the clinical trials on the technology reflect current UK clinical practice?	Yes broadly - though as mentioned patients with prodromal AD are diagnosed clinically usually without access to biomarkers, and there is no pharmacological treatment
18a. If not, how could the results be extrapolated to the UK setting?	
18b. What, in your view, are the most important outcomes, and were they measured in the trials?	See answer to Q7
18c. If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	This is a source of contention. Abnormal amyloid metabolism has been a dominant hypothesis regarding the aetiology of AD for over 30 years and in turn, the possibility of whether modifying this protein can confer meaningful benefits. This is an active area of scientific debate with protagonists and opponents to this hypothesis That said – the phase II and phase III of donanemab together point to a clear dose and time response to the clearance of amyloid as measured by both PET-amyloid and CSF biomarkers. There is an ongoing debate whether the clinical benefit of amyloid reduction is mediated by downstream impacts of other pathological events. (In the future advances in blood biomarkers like p-tau 181 and 217 could mean greater access to biomarkers at lower costs).
18d. Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	Additional safety concerns focus on the potential interaction with other comorbidities and concomitant medications (especially cerebrovascular disease, cerebral amyloid angiopathy, inflammatory vasculitis, and use of anticoagulants. Importantly, there is a need to better understand the risk of mortality: In the donanemab phase III trial three of the sixteen deaths in the treatment arm were attributed to the drug: Sims JR, Zimmer JA, Evans CD, Lu M, Ardayfio P, Sparks JD, et al. Donanemab in Early Symptomatic Alzheimer Disease: The TRAILBLAZER-ALZ 2 Randomized Clinical Trial. *JAMA. 2023;* 10.1001/jama.2023.13239).
19. Are you aware of any relevant evidence that might	No

not be found by a systematic review of the trial evidence?	
20. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance TA217?	No - though similar results to the lecanemab trial has been observed
21. How do data on real-world experience compare with the trial data?	There is very limited real-world data yet. We would advocate the use a common toolkit of clinical assessments and outcome measures across sites delivering donanemab (and subsequent DMTs) as collectively this would support enhanced post-approval outcome and safety monitoring. Indeed, there is a strong argument for a UK wide dementia treatment registry that systematically collects data on patients who are treated (and could be developed in conjunction with Dementia Platforms UK). This would enable longitudinal outcomes to be tracked, analysed and future service and commissioning priorities determined. This surveillance will support openness and transparency about understanding their benefits and risks and help track equality of access. In June 2023 the US Centers for Medicare and Medicaid Services proposed medicare coverage for a mAb with traditional FDA approval will require the treating physician to participate in a registry, though the Alzheimer's Association (who sponsor the Alzheimer's Network for Treatment and Diagnostic (ALZ-NET) registry) expressed concerns about mandating this as a condition of accessing coverage

Equality

22a. Are there any potential equality issues that should be taken into account when considering this treatment?	If specialised, regional hub deliver the medication then it will be essential to ensure inclusive and fair access including underrepresented groups and communities, all ages, and taking into consideration factors such as geographical and socio-economic differences. Clear protocols will be required to ensure care pathways with primary and secondary care are established.
22b. Consider whether these issues are different from issues with current care and why.	Disease modifying treatments targeting the early phases of Alzheimer's disease represent a significant advancement in technology that have the potential to reduce associated morbidity and mortality. There is no current treatment for this phase of the illness, and we anticipate delaying symptoms by at least 5 months (over 18 months of the trials) could offer significant clinical and societal benefits. Donanemab is a monoclonal antibody treatment delivered monthly by intravenous infusion. Current care pathways and access to diagnostic and treatment serviced are limited; preparing the ground for future DMTs and building extra capacity and integration between acute and mental health trusts is likely to be very important. This will build extra clinical and research capacity and expertise to offer such treatments to those who need it the most. In relation to donanemab specifically, there are higher levels of confidence that the medication is biologically active and significant lowers amyloid pathology. However, further evidence is required to determine the longer term clinical benefits and risks of this medication on the natural history of the illness beyond 18 months. We see merit in delivering this medication initially through specialist, regional hub clinics that have access to expertise and governance that will enable safe delivery of this treatment. This would need investment and training so staff can: undertake and process lumbar punctures for CSF, access and interpret amyloid PET imaging, perform repeat MRI imaging, and operate within an integrated MDT to decide on treatment and manage monitoring. It will be crucial to make sure hub access is equitable and that no groups suffer systemic disadvantage in terms of access. This should inform the situation and access arrangements for the hubs. This would provide a 'managed' way to still offer gated access to the medication and allow services to develop their expertise, infrastructure and capacity to deliver this and future DMTs subject to regulatory approvals.

Key messages

23. In up to 5 bullet points, please summarise the key messages of your submission.	1. Statistically significant modest clinical benefits with donanemab were observed across primary and secondary outcome measures as well as clear-cut changes in amyloid levels as the core pathological target. 2. There are important safety concerns that must be considered with a need for clear risk mitigation strategies. 3. Delivering donanemab safely, effectively and equitably will require significant changes in how services are organised. We have described a multi-professional "hub' model as a way to start delivering this treatment within the NHS. However, alongside current waiting lists, the lack of a diagnostic infrastructure for the necessary imaging and molecular biomarkers is likely to be a significant limiting factor in the delivery of donanemab. 4. To tailor and guide decisions about the eligibility for donanemab treatment, we support adopting a framework similar to the "Appropriate Use Recommendations" (adapted for UK use) for lecanemab as described by Cummings et el. We recognise the current evidence to inform longer term therapy decisions is limited and this creates uncertainties about therapy decisions – such as how long to treat? Extrapolating from the findings from the phase III study with donanemab, until more evidence is available, there could be logistical and cost-effective benefits in limiting a course of treatment with donanemab initially to 18 months. (The assumption here is that over this course of treatment an estimated 70-80% of people will become "amyloid negative": for those individuals who reach "remission" we do not know whether prolonged treatment is required, and conversely for those individuals who are "non-responders" and fail to convert after 18 months, it seems unlikely continued use would be beneficial. However, more evidence is required to inform future prescribing). 5. Establishing a nation-wide registry (common database) that captures the use of donanemab (and any subsequent DMT) would offer benefits in monitoring their real-world safety and efficacy outcomes and inform future planning.

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NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Donanemab for treating mild cognitive impairment or mild dementia caused by Alzheimer's disease [ID6222]

Professional organisation submission

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 13 pages.

About you

1. Your name	[redacted]
2. Name of organisation	UCL Dementia Research Centre (DRC)
3. Job title or position	[redacted]
4. Are you (please select Yes or No):	An employee or representative of a healthcare professional organisation that represents clinicians? NO A specialist in the treatment of people with this condition? YES A specialist in the clinical evidence base for this condition or technology? I have knowledge of the evidence base – but not clear if that makes me a specialist Other (please specify):
5a. Brief description of the organisation (including who funds it).	The DRC is a multidisciplinary research centre that is part of University College London's Dept of Neurodegenerative Disease at the Institute of Neurology – UCL is HEFC funded
5b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.] **If so, please state the name of manufacturer, amount, and purpose of funding.**	The DRC has not received funding directly from the manufacturers. I, and other members of the DRC, have provided consultancy (on clinical trial design etc) for the manufacturer. All payments for my consultancy services are made to UCL (via UCL Consultants) and are not taken personally. The amounts are typically less than £1,000.

5c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No

The aim of treatment for this condition

6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	To slow progression
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	A slowing of the rate of progression – at an early (mild dementia) stage of disease – by more than 20% over 18 months or longer.
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes.

What is the expected place of the technology in current practice?

9. How is the condition currently treated in the NHS?	Currently there are only symptomatic treatments. There are three acetylcholinesterase inhibitors (donepezil, rivastigmine and galantaine) and one NMDA receptor antagonist (memantine).
9a. Are any clinical guidelines used in the treatment of the condition, and if so, which?	There are NICE guidelines https://www.nice.org.uk/guidance/ng97 https://www.nice.org.uk/guidance/ta217
9b. Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	The current pathway of care is fairly well defined. It does vary between professionals - e.g on the use of biomarkers to confirm diagnosis. My experience if from within the NHS in England
9c. What impact would the technology have on the current pathway of care?	Major impact on need for precision of diagnosis (e.g. confirmation of amyloid pathology) before treatment and for the monitoring of treatments.
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	There will be significant differences – including as mentioned in 9c above
10a. How does healthcare resource use differ between the technology and current care?	There will be greater need for structural imaging (MRI) and for molecular diagnosis by imaging (amyloid PET) or via amyloid biomarkers (cerebrospinal fluid based measures of amyloid beta 42/40 ratio and phosphor-tau)

10b. In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Specialist clinics initially.
10c. What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	More facilities and training for administration (currently iv) of the medication. More access to MRI for diagnosis and safety monitoring More laboratory facilities and training for CSF biomarker measurement (and in time blood biomarkers)
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes
11a. Do you expect the technology to increase length of life more than current care?	Yes
11b. Do you expect the technology to increase health-related quality of life more than current care?	Yes
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Yes The therapy will be more likely to be appropriate in younger AD patients with fewer co-morbidities and fewer co-pathologies.

The use of the technology

13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	More difficult. There are many practical implications – including being able to recognise side effects (e.g. ARIA) and to manage these safely.
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Yes and yes.
15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	The benefit for carers and family members should be included.

16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	Yes – this is innovative in terms of offering slowing of disease progression – a need that is not currently met.
16a. Is the technology a 'step-change' in the management of the condition?	Yes
16b. Does the use of the technology address any particular unmet need of the patient population?	As above
17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	There is considerable burden associated with regular iv infusions – the current mode of administration. There is a significant risk of side effects (e.g. ~20% risk of ARIA) that will cause additional burden (extra scans, anxiety). A small proportion of these (about 20% of those who develop ARIA) will have symptoms.

Sources of evidence

18. Do the clinical trials on the technology reflect current UK clinical practice?	This is a novel treatment – and a) the precision of diagnosis (biomarker supported) and b) the level and frequency of monitoring in the trials are not current UK clinical practice
18a. If not, how could the results be extrapolated to the UK setting?	The resource implications of monitoring can be modelled
18b. What, in your view, are the most important outcomes, and were they measured in the trials?	The most important outcomes were clinical (both in terms of patient function and carer burden) and were measured in the trials.
18c. If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	The primary outcome was clinical (not surrogate)
18d. Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	None that were not known – but treatment with thrombolysis has since been shown to be very dangerous.
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No.

20. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance TA217	None relevant
21. How do data on real-world experience compare with the trial data?	Currently limited

Equality

22a. Are there any potential equality issues that should be taken into account when considering this treatment?	Yes 1. Patients **who do not have a partner** or relative who could help facilitate timely diagnosis and treatment are likely to be disadvantaged. 2. Groups where diagnosis is typically delayed – a) lower levels of medical literacy, English as a second language; b) lack of effective advocate; c) greater stigma around dementia – all of which delay diagnosis and the window for treatment (very early disease) will be missed. 3. If cut-offs for treatment are based on criteria in the trials then tests (e.g MMSE) for eligibility where scores are lower in those with **poorer education** will lead to those individuals not getting therapy
22b. Consider whether these issues are different from issues with current care and why.	The difference here is that the window for treatment is limited – and timely diagnosis is much more important than currently.

Key messages

23. In up to 5 bullet points, please summarise the key messages of your submission.	• The first disease progression slowing therapy for AD (the most common cause of dementia) is a step change in what can be done. • There are very significant burdens for patients and families (e.g. frequent iv infusions, MRI scans). • There are significant side effects and risks – especially outside a controlled trial setting. • Timely and precise diagnosis will require major changes in NHS provision – and there is a risk of inequitable access. • Major education and training will be needed in specialist centres – but also for those seeing individuals in A&E who have side effects

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

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NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Donanemab for treating mild cognitive impairment or mild dementia caused by Alzheimer's disease [ID6222]

NHS organisation submission (ICBs and NHS England)

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you

1. Your name	[redacted]
2. Name of organisation	NHS England
3. Job title or position	[redacted]

4. Are you (please select Yes or No):	Commissioning services for an ICB or NHS England in general? Yes or No Commissioning services for an ICB or NHS England for the condition for which NICE is considering this technology? Yes or No (PET-CT and APOE-4 Genetic Testing) Responsible for quality of service delivery in an ICB (for example, medical director, public health director, director of nursing)? Yes or No An expert in treating the condition for which NICE is considering this technology? Yes or No An expert in the clinical evidence base supporting the technology (for example, an investigator in clinical trials for the technology)? Yes or No Other (please specify):
5a. Brief description of the organisation (including who funds it).	NHS England purpose is to lead the NHS in England to deliver high-quality services. We work with the wider NHS, national partner organisations and other key stakeholders to optimise outcomes and patient experience through expert clinical leadership, the use of digital technology, research and innovation, and the delivery of value for money and increased productivity and efficiency for all. The establishment of integrated care boards within integrated care systems, which are made up of public services that provide health and care, means that NHS England is changing the way it works to best support and empower local system partners to deliver on their responsibilities. We work with, and support, regional and ICB leadership teams in the commissioning of high-quality services. Our NHS England Operating Framework sets out how we are supporting systems and providers to lead locally to improve the health of the population, improve the quality of patient care, tackle inequalities and deliver care more efficiently. It describes our six longer-term aims: 1. Longer healthy life expectancy. 2. Excellent quality, safety and outcomes. 3. Excellent access and experience. 4. Equity of healthy life expectancy, quality, safety, outcomes, access and experience. 5. Value for taxpayers' money. 6. Support to society, the economy and environment.
5b. Do you have any direct or indirect links with, or funding from, the tobacco industry?	None

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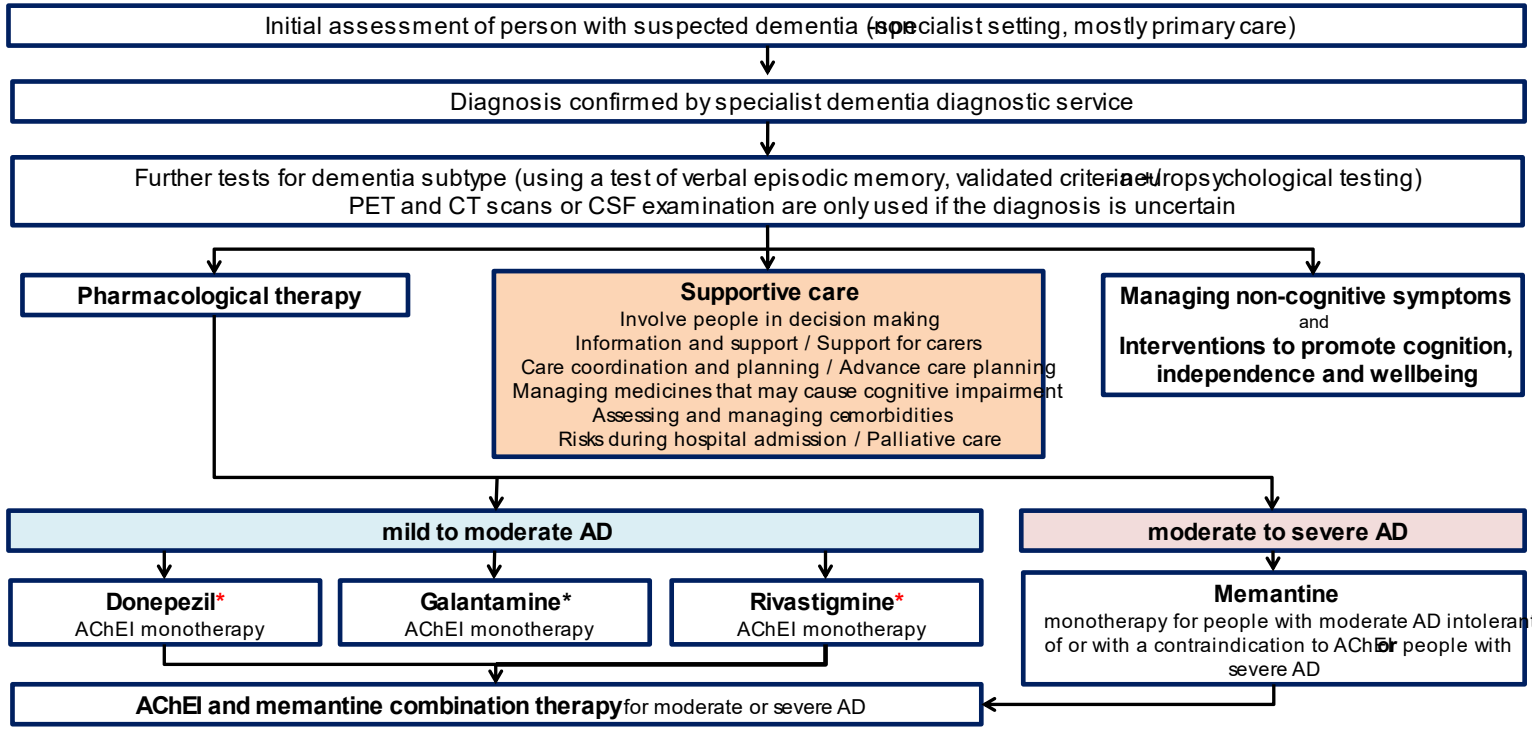
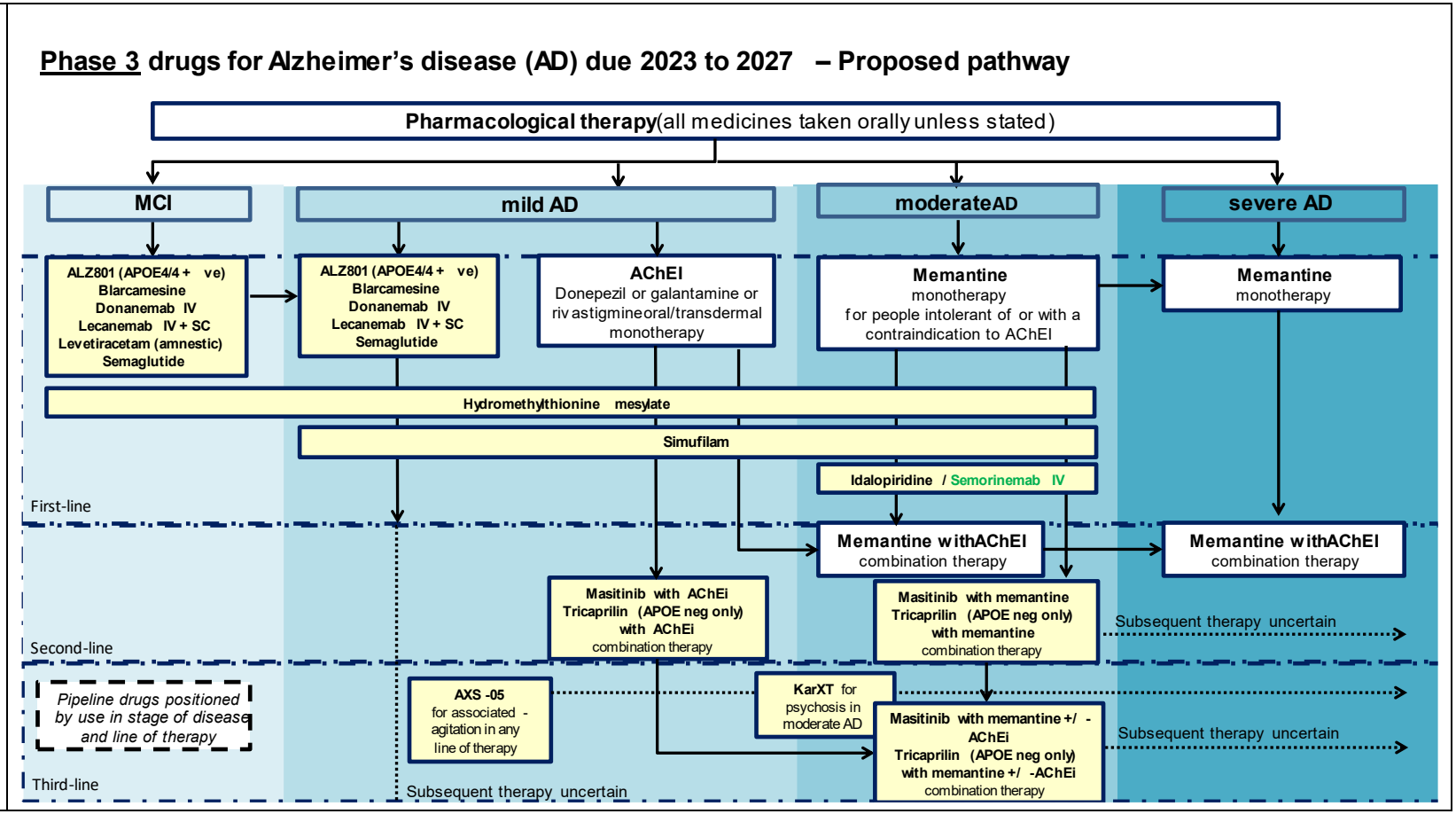
Current treatment of the condition in the NHS

6. Are any clinical guidelines used in the treatment of the condition, and if so, which?	There are three NICE clinical guidelines published on this topic:- • https://www.nice.org.uk/guidance/ng127 • https://www.nice.org.uk/guidance/ng97 • https://www.nice.org.uk/guidance/ng16 There is one current Technology Appraisal published on this topic:- https://www.nice.org.uk/guidance/ta217

7. Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	The current Alzheimer's disease pathway is currently well defined and horizon scanning undertaken by the Specialist Pharmacy Service (SPS) (see below) has provided an overview. Pharmacological management is currently being provided within the care pathway, but it is worth noting that this is most typically in more advanced stages of Alzheimer's disease and that supportive care and interventions to promote cognition, independence and wellbeing are also vital to improving patient outcomes. There is variation in the speed and access to dementia services (including diagnosis) across the NHS. **Alzheimer's disease (AD) – Current pathway**  www.nice.org.uk/guidance/conditions-and-diseases/mental-health-and-behavioural-conditions/dementia

8. What impact would the technology have on the current pathway of care?	SPS horizon scanning has highlighted that the dementia pharmacological treatment pathway has the potential to be significantly reformed (see diagram below) should the forthcoming pipeline of products in late-stage trials receive marketing authorisation(s) and subsequently be recommended as clinically and cost-effective by NICE. Products such as donanemab are being initially developed for mild cognitive impairment (MCI) associated with AD and mild AD, which will result in patients with earlier / milder forms of Alzheimer's coming forward for assessment and being eligible for potential treatment with disease modifying therapies (DMTs). There are a number of key changes in service capacity and delivery, which would result from the availability of products such as donanemab, due to the requirements to identify, assess, test, deliver treatment and monitor patients. The administration and logistics of ensuring a seamless transition between these elements should also be considered carefully. • Increase in demand on primary care teams as awareness of MCI and DMT treatment options increases • Increase in demand into memory clinics or other local services as awareness of MCI and DMT treatment options increases and additional patients are referred for assessment • New neurology / psychiatry / geriatric medicine clinics being established • Increase in PET-CT and lumbar puncture capacity, neither of which are currently routinely used in the diagnosis of Alzheimer's. There may also be demand for PET-CT or other diagnostic approaches in monitoring for amyloid clearance during treatment. • Increase in MRI capacity (both as a baseline diagnostic tool and as part of safety monitoring during treatment) • New requirement for amyloid radiotracer supply • Expansion of genetic testing (with a new standalone APOE-4 test requirement),associated information provision for family members and counselling services • Increases in demand on secondary or community based infusion services and additional IV capacity requirements • Increases in demand on primary care and secondary care services in the identification and management of ARIA



The use of the technology

9. To what extent and in which population(s) is the technology being	Donanemab is not currently being utilised in the NHS.

used in your local health economy?	
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Please see section 8 above for further details – donanemab would require a new diagnostic and treatment pathway to accommodate the product. ICBs may choose to adapt current services (for example expanding the scope and capacity of local memory clinics) or commission new bespoke services to accommodate the specific needs of the specific 'early Alzheimer's' cohort and the associated diagnostic, treatment and monitoring requirements.
10a. How does healthcare resource use differ between the technology and current care?	Please see section 8 above for further details – donanemab would be associated with significant additional resource requirements should NICE recommend the technology as a clinically and cost-effective use of NHS resources. This is because we would expect an increased number of patients to present with earlier signs and symptoms that are potentially indicative of AD and also because there are additional diagnostic, treatment and monitoring requirements over and above current treatment options.
10b. In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	As a new medicine, donanemab is anticipated to be initiated and monitored in a secondary care clinic setting. However, it is important to note that the initial assessment and referral of patients will be likely to be largely undertaken within primary care and that many other elements of the pathway will be delivered by local / community services (such as MRIs being undertaken in community diagnostic centres). Alongside its wider system leadership role, NHS England has direct (national) commissioning responsibility for PET-CT and genomic testing. All other elements of the pathway fall within ICB commissioning responsibilities.
10c. What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	There is a need for substantial staffing, training and infrastructure investment to deliver these new treatments. Please refer to section 8 for further details. Current dementia treatments are oral, initiated by specialists and then prescribed in primary care under a shared-care protocol. Donanemab will need investment in services and staff to allow delivery of IV infusions and monitoring for (and management of) ARIA. Presence of amyloid beta pathology must be confirmed before starting treatment. A stand-alone test for ApoE ε4 in dementia is not currently listed in National Genomic Test Directory. GPs will need upskilling in early patient identification; and adapted (or new) community assessment and diagnostic pathways will be needed to identify amyloid-positive MCI.
10d. If there are any rules (informal or formal) for starting and stopping treatment with the technology, does	After initial specialist assessment (which includes clinical history taking, neurological examination and cognitive testing), dementia subtype may be diagnosed using a test of verbal episodic memory, validated criteria +/- neuropsychological testing. CT scans are currently more typically used that MRI, and PET-CT or lumbar puncture (including CSF examination) are only currently used by exception in routine care if the diagnosis is uncertain. Significant diagnostic pathway changes and capacity increases would be needed for donanemab. A test for ApoE

this include any additional testing?	ε4 in dementia is not currently listed in the National Genomic Test Directory and this would therefore need to be newly commissioned. Amyloid PET-CT is also not currently routinely commissioned by NHS England. The current long-term clinical data associated with donanemab (and other disease-modifying pipeline products) is limited and therefore identifying formal stopping rules for treatment is challenging.
11. What is the outcome of any evaluations or audits of the use of the technology?	N/A

Equality

12a. Are there any potential equality issues that should be taken into account when considering this treatment?	It is important to note that the epidemiology with MCI and mild Alzheimer's disease remains highly uncertain and therefore it is not clear how many patients will present and be referred for assessment (or take up) treatment with donanemab. There are known differences in Alzheimer's prevalence between ethnic groups. It is not clear how patients would be clinically prioritised if demand for the technology is greater than the NHS capacity to deliver treatment. It should also be noted that existing local variation in the capacity of primary care practice, memory clinics, diagnostics and infusion services is likely to impact the number of patients treated and the pace of service mobilisation.
12b. Consider whether these issues are different from issues with current care and why.	Donanemab is one of a number of new products coming to the market which have the potential to significantly alter the care pathway and therefore it is difficult to comment at this stage. There is a significant pipeline of potentially disease modifying treatments for AD in late-stage trials.

Thank you for your time.

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NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Donanemab for treating mild cognitive impairment or mild dementia caused by Alzheimer's disease [ID6222]

Clinical expert statement

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Do not include medical information about yourself or another person that could identify you or the other person.

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Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

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Please underline all confidential information, and separately highlight information that is submitted as 'confidential [CON]' in turquoise, and all information submitted as 'depersonalised data [DPD]' in pink. If confidential information is submitted, please also send a second version of your comments with that information redacted. See Health technology evaluations: interim methods and process guide for the proportionate approach to technology appraisals (section 3.2) for more information.

The deadline for your response is **5pm** on **<insert deadline>.** Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

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

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

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Part 1: Treating Alzheimer's disease and current treatment options

Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality

1. Your name	Nick Fox
2. Name of organisation	Dementia Research Centre, UCL Queen Square Institute of Neurology
3. Job title or position	Professor of Neurology, Hon Consultant Neurologist
4. Are you (please tick all that apply)	☐ An employee or representative of a healthcare professional organisation that represents clinicians? ☒ A specialist in the treatment of people with Alzheimer's disease? ☒ A specialist in the clinical evidence base for Alzheimer's disease or technology? ☐ Other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☒ Yes, I agree with it ☐ No, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ Other (they did not submit one, I do not know if they submitted one etc.)
6. If you wrote the organisation submission and/or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission)	☐ Yes
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
8. What is the main aim of treatment for Alzheimer's disease?	Slow or delay progression and thereby maintain functional independence for as long as possible

(For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	
9. What do you consider a clinically significant treatment response? (For example, a reduction in disease activity by a certain amount) • The expert assessment group (EAG) note that the company consider a greater than 20% slowing of clinical progression to be a clinically meaningful benefit whereas a publication presenting the European consensus on disease-modifying trials in Alzheimer's disease states that a reduction in the rate of disease progression of 30% to 50% is a reasonable goal. Please provide your view on what a clinically meaningful benefit. • What would be the most appropriate outcome measure to capture and model the effects of treatment on changes in the cognition and function of people with MCI and mild dementia due to Alzheimer's disease (EAG Key issue 2)?	I believe 20% (or greater) slowing of progression is clinically significant. However, this does have some caveats: it depends on how long the slowing is sustained for and at what stage in the disease. a) I think that 20% or more slowing sustained for 18 months or more is clinically significant. b) I think that 20% slowing for this period or longer is clinically significant if it applies while individuals are in the mild to moderate stages of disease. I think it is also worth noting that international consortia such as ADNI (the Alzheimer's Disease Neuroimaging initiative) have consistently used 20 to 25% slowing of progression for sample size estimates – these are regarded by the field as a meaningful slowing of progression. Schott JM et al - Neurobiology of Aging 31 (2010) 1452–62 https://doi.org/10.1016/j.neurobiolaging.2010.04.011 Hua et al NeuroImage Volume 51, Issue 1, 15 May 2010, Pages 63-75 Furthermore, my conversations with my patients and their families suggest that the amount of additional time gained in a relatively functionally independent stage of the disease is the most easily understood by families as clinically meaningful. A 4-5 months delay (or 4-5 months longer in a milder stage) over 18 months is (in my view) a clinically meaning benefit. I think the CDR Sum of Boxes (CDR-SB) is probably the most appropriate outcome measure. Measures of activities of daily living are also appropriate and have complementary value.
10. In your view, is there an unmet need for patients and healthcare professionals in Alzheimer's disease?	Yes, most definitely. My patients and their families are desperate to have something that slows progression and reduces the loss of functional

• Considering the progression of Alzheimer's disease, is the background mortality risk expected to increase with increasing disease severity or remain the same from MCI to severe Alzheimer's disease (EAG Key issue 6)?	independence. Evidence for this is their willingness to try untested therapies (suggested on the internet) or to pay privately for these treatments. Furthermore many have asked me since the FDA approval of lecanemab whether they should try and fly to the US to get treatment – including those who really cannot afford that. The background mortality risk increases greatly as people move into more severe stages of disease. There is probably a slight (but only slight) in going from MCI to mild AD. The biggest increase is when people move to the level of severity where their communication reduces - and even more so once they have impaired mobility and reduced awareness of swallowing – both of which increase the risk of infections.
11. How is Alzheimer's disease currently treated in the NHS? • Are any clinical guidelines used in the treatment of the condition, and if so, which? • Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.) • What impact would the technology have on the current pathway of care? • The EAG note that acetylcholinesterase inhibitors and/or memantine are used off-label including in people with mild cognitive impairment (MCI) due to probable Alzheimer's disease (EAG Key issue 1). Do you consider that use of these treatments has a potential impact on measures of cognition and function in people with MCI or mild dementia due to probable Alzheimer's disease?	Yes. The NICE guideline. This recommends the use of acetyl choline esterase inhibitors and memantine. The pathway of care is fairly well defined. There are however varying local arrangements for referrals and who should deliver care - for example individuals with young onset (<65y) AD are more likely to be referred to a neurology service – but this varies regionally. There are also very different delays in diagnosis. In some services most care is delivered by nurses. Most NHS professionals would aim to follow NICE guidance. The major impact would be to increase the urgency of diagnosis and the urgency of starting treatment. The current delay from symptoms to diagnosis is typically three years – some of that delay is because individuals do not seek help but there are also delays at primary care level and then after being referred on. Unlike cancer there is not a sense of urgency to make a diagnosis in dementia – largely because our current therapies for AD are only of symptomatic benefit and so it is not obvious how important any delay might be. This will change if there is a narrow window of severity when people are eligible for a disease modifying therapy.

	I do believe that acetylcholinesterase inhibitors and memantine have a potential impact on measures of cognition and function in mild AD (the trials support this). It is probable that they also have an impact at the MCI (due to AD) stage but this is not established.
12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice? • How does healthcare resource use differ between the technology and current care? • In what clinical setting should the technology be used? (for example, primary or secondary care, specialist clinic) • What investment is needed to introduce the technology? (for example, for facilities, equipment, or training)	The technology (donanemab) is not yet used. It will be used in a different way to current care. Notably: a) A molecular specific (amyloid positive) diagnosis of AD will now be needed (rather than just desirable). This is already done in specialist centres but not done in most services. This is likely to be with CSF or new blood tests (given the lack of PET capacity) b) An MRI scan will be needed for eligibility – current NICE guidance suggests either CT or MRI scan can be used in diagnosis. Facilities to deliver infusions will be needed in secondary care Increased capacity to analyses CSF (or blood) tests will be needed – this could be scaled up relatively easily with a small number of centralised labs Increased MRI capacity (and/or better use with rapid imaging) will be needed
13. Do you expect the technology to provide clinically meaningful benefits compared with current care? • Do you expect the technology to increase length of life more than current care? • Do you expect the technology to increase health-related quality of life more than current care? • If you have any experience of using donanemab, please provide your view on the likelihood and extent of potential long-term treatment effects, including those	Yes I do expect the technology (donanemab) to provide clinically meaningful benefits compared with current care. I believe this strongly. I do expect the technology to increase length of life I do expect the technology to increase health-related quality of life more than current care I also believe the technology will increase health-related quality of life for those who care for people with AD (e.g. a spouse or partner).

that might persist after treatment has stopped (EAG Key issue 7).	My reading of the clinical trial data and long term extension studies for the anti-amyloid monoclonals very much support a persistent effect once treatment has stopped.
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population? • Please provide your view of the balance between potential risks and benefits of donanemab treatment. In particular, please consider people who are homozygous for the APOE ε4 allele (EAG Key issue 5).	Those who are frail are less likely to cope with the demands of treatment. I think the risks are manageable and do not outweigh the benefits. There clearly are greater risks of ARIA-E for those who are homozygous for the E4 allele – however these risks are manageable – and occur early in treatment. It will be important to counsel individuals about the risk to ensure appropriate informed consent. It is notable that individuals were very keen to enrol into these trials when the risks were known and the benefits not yet proven. Now the clnical benefit has been shown and we have many (and growing) person-years of experience of managing ARIA. I believe that shifts the risk-benefit balance further towards benefit. The clinical use of anti-amyloid therapies (e.g. lecanemab in the US and Japan) will further increase our knowledge of risk management.
15. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use? (For example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed)	It will be more difficult for healthcare professionals. Increased monitoring for ARIA in particular.
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Yes. Eligibility will need clinical assessment and also MRI and a measure of amyloid (CSF, PET – or soon plasma).
17. Do you consider that the use of the technology will result in any substantial health-related benefits that	I think the technology will give substantial health-related benefits to family members who deliver the majority of care for those with AD.

are unlikely to be included in the quality-adjusted life year (QALY) calculation? • Do the instruments that measure quality of life fully capture all the benefits of the technology or have some been missed? For example, the treatment regimen may be more easily administered (such as an oral tablet or home treatment) than current standard of care	
18. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met? • Is the technology a 'step-change' in the management of the condition? • Does the use of the technology address any particular unmet need of the patient population?	Yes. This is definitely a step change. This has been long awaited and is much needed. Slowing progression when people are in the mild stages of the disease has been a focus of research for decades – and finally we have a therapy that can slow progression and maintain people for longer when they still are functionally independent.
19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	The burden of having to have regular infusions does have a negative impact. There is also a negative impact on quality of life while ARIA-E is present in those who develop it (80% are asymptomatic) mainly due to increased MRI monitoring.
20. Do the clinical trials on the technology reflect current UK clinical practice? • If not, how could the results be extrapolated to the UK setting? • What, in your view, are the most important outcomes, and were they measured in the trials? • If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes? • Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	Yes. The most important outcomes were measured in the trials. In my view the CDR-SB, and the ADL measures were the more important. Measures of carer burden are also important for the wider impact. No adverse effects that have come to light subsequently.

21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	The unpublished (but presented) long term extension data from other monoclonals.
22. How do data on real-world experience compare with the trial data?	
23. NICE considers whether there are any equalities issues at each stage of an evaluation. Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics. Please state if you think this evaluation could • exclude any people for which this treatment is or will be licensed but who are protected by the equality legislation • lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population • lead to recommendations that have an adverse impact on disabled people. Please consider whether these issues are different from issues with current care and why.	As ever those who have not got an advocate are likely to disadvantaged.

More information on how NICE deals with equalities issues can be found in the NICE equality scheme. Find more general information about the Equality Act and equalities issues here.	

Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

Click or tap here to enter text.

Click or tap here to enter text.

Click or tap here to enter text.

Click or tap here to enter text.

Click or tap here to enter text.

Thank you for your time.

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Part 1: Treating Alzheimer's disease and current treatment options

Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality

1. Your name	Tomas James Welsh
2. Name of organisation	RICE – The Research Institute for the Care of Older People
3. Job title or position	Research and Medical Director / Consultant Geriatrician
4. Are you (please tick all that apply)	☐ An employee or representative of a healthcare professional organisation that represents clinicians? ☒ A specialist in the treatment of people with Alzheimer's disease? ☐ A specialist in the clinical evidence base for Alzheimer's disease or technology? ☐ Other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☒ Yes, I agree with it ☐ No, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ Other (they did not submit one, I do not know if they submitted one etc.)
6. If you wrote the organisation submission and/or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission)	☒ Yes
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	N/A
8. What is the main aim of treatment for Alzheimer's disease?	In my view the aim of the treatment of Alzheimer's disease (AD) is to maintain function, and slow disease progression (i.e. reduce the risk of severe disease with marked functional impact). For geriatricians, AD significantly contributes to

(For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	later-life rates of institutionalisation, frailty, falls, continence issues and other geriatric syndromes associated with diminished quality of life. These remain pertinent outcomes.
9. What do you consider a clinically significant treatment response? (For example, a reduction in disease activity by a certain amount) • The expert assessment group (EAG) note that the company consider a greater than 20% slowing of clinical progression to be a clinically meaningful benefit whereas a publication presenting the European consensus on disease-modifying trials in Alzheimer's disease states that a reduction in the rate of disease progression of 30% to 50% is a reasonable goal. Please provide your view on what a clinically meaningful benefit. • What would be the most appropriate outcome measure to capture and model the effects of treatment on changes in the cognition and function of people with MCI and mild dementia due to Alzheimer's disease (EAG Key issue 2)?	Defining a clinically meaningful outcome in the context of a heterogenous, progressive disease is highly challenging. In practice a number of scales are regularly used in clinical trials to try to capture change in cognition and function. The scales that have been used in the trials of this compound – e.g. CDR-SB are not unreasonable and are widely used in research if not in clinical practice. There is ongoing debate about what constitutes a clinically meaningful response to treatment. Given the complex nature of the disease process and the timescales over which the disease develops, it seems unlikely that a single compound will result in dramatic changes in outcomes over a relatively short period. A slowing of over 20% may be meaningful in the right context but critically any benefit must be weighed against potential adverse effects. A time-to-event analysis may be another valid method to evaluate the effect size.
10. In your view, is there an unmet need for patients and healthcare professionals in Alzheimer's disease? • Considering the progression of Alzheimer's disease, is the background mortality risk expected to increase with increasing disease severity or remain the same from MCI to severe Alzheimer's disease (EAG Key issue 6)?	There is a clear, significant, unmet need for people with Alzheimer's disease. Diagnostic services are variable across the country. Access to basic imaging and interpretation is variable. Access to advanced imaging (e.g. FDG-PET) or CSF biomarkers is even more patchy. Current treatments provide mild symptomatic benefits only and again there is huge variation in the pathways for accessing drug treatment. Non-drug treatment such as cognitive stimulation therapy, although recommended by NICE, is not available in multiple NHS settings.

	With regards to the question about mortality, mortality rates are higher in people with more advanced stages of the disease.
11. How is Alzheimer's disease currently treated in the NHS? • Are any clinical guidelines used in the treatment of the condition, and if so, which? • Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.) • What impact would the technology have on the current pathway of care? • The EAG note that acetylcholinesterase inhibitors and/or memantine are used off-label including in people with mild cognitive impairment (MCI) due to probable Alzheimer's disease (EAG Key issue 1). Do you consider that use of these treatments has a potential impact on measures of cognition and function in people with MCI or mild dementia due to probable Alzheimer's disease?	Both NICE and the Scottish Intercollegiate Guideline Network (SIGN) produce widely used guidance on the treatment of dementia due to AD. Diagnostic and treatment pathways for Alzheimer's disease and other causes of cognitive impairment are highly variable across the country and, in the view of many, routinely underfunded. There are significant challenges accessing timely and accurate diagnosis (please see the Alzheimer's Society Consensus Statement). There is significant variation in diagnostic rates of causes of dementia (as demonstrated in multiple previous national memory service audits). Treatment guidelines are formulated by stage of disease rather than the underlying cause (i.e. dementia / MCI rather than Alzheimer's disease / fronto-temporal degeneration etc). This complicates matters significantly. This technology would require significant, but desperately needed, investment in the care pathway, workforce, training, facilities, equipment etc. to be operationalised. At present research active centres are best place to deliver this treatment should it be licensed. Guidance on Mild Cognitive Impairment (MCI) is needed and this could include the value (or not) of cognitive enhancing medication. I understand this has been raised with NICE recently. Evidence of benefit for the cognitive enhancers in people with MCI due to AD is limited but these medications are being used in this context off-label. Further trials to resolve this question would be helpful but are unlikely to be funded.
12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	This technology will require major changes for delivery. It requires, amongst many other things, access to appropriately trained staff, access to advanced diagnostics (potentially including CSF sampling), access to MRI scanning for safety screening and monitoring and the healthcare staff to complete the scans

• How does healthcare resource use differ between the technology and current care? • In what clinical setting should the technology be used? (for example, primary or secondary care, specialist clinic) • What investment is needed to introduce the technology? (for example, for facilities, equipment, or training)	and to interpret them. It requires a cultural shift from a largely clinically based diagnostic pathway with a focus on 'dementia' diagnosis to a biological-clinical diagnosis with a focus on a timely accurate diagnosis of the underlying condition before the disease has reached the stage of dementia. This technology should be delivered in secondary care Multiple areas of investment are needed. These include but are not limited to - Workforce, facilities, equipment (diagnosis, treatment delivery, safety scanning)
13. Do you expect the technology to provide clinically meaningful benefits compared with current care? • Do you expect the technology to increase length of life more than current care? • Do you expect the technology to increase health-related quality of life more than current care? • If you have any experience of using donanemab, please provide your view on the likelihood and extent of potential long-term treatment effects, including those that might persist after treatment has stopped (EAG Key issue 7).	It is unclear whether this treatment will increase life expectancy, and its aim, to my mind, is more around slowing disease progression and improved function. Longer term outcomes are unclear. It is plausible that, if these medications are truly disease modifying, that there may be an impact on quality of life. AD is a common thread in multiple health problems of older age such as falls and frailty. A medication that potentially alters the disease trajectory could reap significant benefits outside of a narrow cognitive focus. I have trial experience of this medication and of similar trial compounds. I would defer to the published trial results here.
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population? • Please provide your view of the balance between potential risks and benefits of donanemab treatment. In particular, please consider people who are	It seems increasingly clear that these potentially disease modifying treatments appear to be more effective when given at biologically earlier stages of the disease. This poses a challenge as the biological stage of the disease does not necessarily align with the symptomatic stage of the disease.

homozygous for the APOE ε4 allele (EAG Key issue 5).	The most commonly discussed side effect of this class of medications is the risk of Amyloid Related Imaging Abnormalities (ARIA). This can take the form of oedema (ARIA-E) or haemorrhage (ARIA-H). In TRAILBLAZER2 6.1% of all donanemab-treated patients had symptomatic ARIA-E (25.4% of all ARIA-E cases). Although first events of ARIA-E resolved in 98% of the cases after a mean of 72.4 days. ARIA-H was observed in 36.4% of all treated patients and 13.6% in the placebo group. Intracranial hemorrhage occurred in 0.4% of treated cases (3 of 853) and in 0.2% of the placebo group (2 of 874). Three participants in the donanemab group died in relation to: severe ARIA-E, severe ARIA-E and ARIA-H, and severe ARIA-E and ARIA-H with intracranial hemorrhage. Two were APOE4 heterozygous carriers. There appear to be higher risks of significant side effects (ARIA) in people who are homozygous for APOE ε4 (ARIA-E occurred in 40.6% of APOE4 homozygous (15.7% in non-carriers)). Significant adverse events have fortunately been rare and the underlying mechanisms and risk factors of these warrant further investigation. These risks must be balanced against modest benefits but of course in the context of a currently incurable, terminal disease. Careful individualised risk assessment, discussion, and risk communication will be needed on a person-by-person basis.
15. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use?	At present there is limited resource in the majority of memory diagnostic and treatment centres. Adapting to implement this new technology will require significant investment as has been discussed already.

(For example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed)	
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Appropriate use recommendations will be needed to guide the use of this technology. Proposals for the use of lecanameb (a similar compound) are already published and in use in the USA. Additional testing will be needed to confirm the diagnosis – either specialist imaging (amyloid PET) or CSF sampling and testing.
17. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation? • Do the instruments that measure quality of life fully capture all the benefits of the technology or have some been missed? For example, the treatment regimen may be more easily administered (such as an oral tablet or home treatment) than current standard of care	Standard quality of life measures may struggle to reflect quality of life in the context of a progressive, debilitating illness such as AD. Home treatment may become an option in the future for this treatment.
18. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met? • Is the technology a 'step-change' in the management of the condition? • Does the use of the technology address any particular unmet need of the patient population?	This technology is a step-change in the management of Alzheimer's disease. This is one of the first potentially disease modifying treatments for this condition. At present only symptomatic treatments are available. This technology addresses a clear unmet need in this population.

19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	
20. Do the clinical trials on the technology reflect current UK clinical practice? • If not, how could the results be extrapolated to the UK setting? • What, in your view, are the most important outcomes, and were they measured in the trials? • If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes? • Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	The trial findings are applicable to UK patients. A number of UK sites have participated in the delivery of the trials of this compound. The huge challenge is that the majority of memory assessment services and national targets are set up around the diagnosis of dementia rather than early detection and subtype diagnosis. A dramatic shift will need to occur to allow timely and accurate diagnosis. This will need resource, good will, and input from a wide spectrum of healthcare providers. Barriers such as divisions between mental health and physical health healthcare providers will need to be bridged. Long term outcomes are still unclear.
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
22. How do data on real-world experience compare with the trial data?	No real-world data for this compound are yet available to my knowledge
23. NICE considers whether there are any equalities issues at each stage of an evaluation. Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged.	Age remains the biggest risk factor for developing Alzheimer's disease and for the majority of older people who do develop the condition multi-morbidity is the normal health status. For many reasons trial populations tend to differ from 'normal' patient populations and in this case this holds true. An age limit was applied to recruitment and the average age of trial participants in TRAILBLAZER2 was 73 (c.f. most memory clinic populations 85). One of my concerns around this technology is the risk that focus will move to younger, fitter individuals and the majority of older people who develop AD or those who present with more advanced AD will lose out on support and treatments.

Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics. Please state if you think this evaluation could • exclude any people for which this treatment is or will be licensed but who are protected by the equality legislation • lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population • lead to recommendations that have an adverse impact on disabled people. Please consider whether these issues are different from issues with current care and why. More information on how NICE deals with equalities issues can be found in the NICE equality scheme. Find more general information about the Equality Act and equalities issues here.	Treatment advances must be incorporated into gerontological attuned person-centred care for older adults with AD.

Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

This medication represents a potential step-change in the management of Alzheimer's disease.
In the context of rare but potentially significant side effects, there are data demonstrating statistically significant, if modest, benefits over placebo.
The advent of potentially disease modifying treatments for AD is to be welcomed but the real-world benefit of these medications, particularly for older adults, is yet to be determined.
Diagnostic and treatment advances must be integrated with gerontologically attuned, person centred care for older adults with AD.
Significant investment will be needed to deliver this treatment at scale.

Thank you for your time.

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NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Donanemab for treating mild cognitive impairment or mild dementia caused by Alzheimer's disease [ID6222]

Patient expert statement

Thank you for agreeing to give us your views on this treatment and its possible use in the NHS.

Your comments are really valued. You can provide a unique perspective on conditions and their treatment that is not typically available from other sources

Information on completing this form

In part 1 we are asking you about living with Alzheimer's disease or caring for a patient with Alzheimer's disease. The text boxes will expand as you type.

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Please use this questionnaire with our hints and tips for patient experts. You can also refer to the Patient Organisation submission guide. **You do not have to answer every question** – they are prompts to guide you. There is also an opportunity to raise issues that are important to patients that you think have been missed and want to bring to the attention of the committee.

NICE National Institute for Health and Care Excellence

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Your response should not be longer than 15 pages.

The deadline for your response is **5pm** on **Friday 31 May.** Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

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

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Patient expert statement

Part 1: Living with this condition or caring for a patient with Alzheimer's disease

Table 1 About you, Alzheimer's disease, current treatments and equality

1. Your name	David Thomas
2. Are you (please tick all that apply)	☐ A patient with Alzheimer's disease? ☐ A patient with experience of the treatment being evaluated? ☐ A carer of a patient with Alzheimer's disease? ☒ A patient organisation employee or volunteer? ☐ Other (please specify):
3. Name of your nominating organisation	Alzheimer's Research UK
4. Has your nominating organisation provided a submission? (please tick all options that apply)	☐ No (please review all the questions and provide answers when possible) ☐ Yes, my nominating organisation has provided a submission ☐ I agree with it and **do not wish to** complete a patient expert statement ☒ Yes, I authored / was a contributor to my nominating organisations submission ☒ I agree with it and **do not wish to** complete this statement ☐ I agree with it and **will be** completing
5. How did you gather the information included in your statement? (please tick all that apply)	☐ I am drawing from personal experience ☒ I have other relevant knowledge or experience (for example, I am drawing on others' experiences). Please specify what other experience: commissioned research into public opinions, conversations with trial participants and people with lived experience. ☐ I have completed part 2 of the statement **after attending** the expert

Patient expert statement

	engagement teleconference ☐ I have completed part 2 of the statement **but was not able to attend** the expert engagement teleconference ☐ I have not completed part 2 of the statement
6. What is your experience of living with Alzheimer's disease? **If you are a carer (for someone with Alzheimer's disease) please share your experience of caring for them**	
7a. What do you think of the current treatments and care available for Alzheimer's disease on the NHS? **7b. How do your views on these current treatments compare to those of other people that you may be aware of?**	
8. If there are disadvantages for patients of current NHS treatments for Alzheimer's disease (for example, how they are given or taken, side effects of treatment, and any others) please describe these	
9a. If there are advantages of donanemab over current treatments on the NHS please describe these. For example, the effect on your quality of life, your ability to continue work, education, self-care, and care for others? **9b. If you have stated more than one advantage, which one(s) do you consider to be the most important, and why?** **9c. Does donanemab help to overcome or address any of the listed disadvantages of current treatment**	

that you have described in question 8? If so, please describe these 9d. If you are able to comment on this, what would you consider to be a clinically meaningful benefit that you have seen (or would hope to see) with donanemab treatment? How would you recognise any benefit of treatment? For example, you might wish to consider particular symptoms of Alzheimer's disease getting better or not getting worse.	
10. If there are disadvantages of donanemab over current treatments on the NHS please describe these. For example, are there any risks with donanemab? If you are concerned about any potential side effects you have heard about, please describe them and explain why	
11. Are there any groups of patients who might benefit more from donanemab or any who may benefit less? If so, please describe them and explain why Consider, for example, if patients also have other health conditions (for example difficulties with mobility, dexterity or cognitive impairments) that affect the suitability of different treatments	
12. Are there any potential equality issues that should be taken into account when considering Alzheimer's disease and donanemab? Please explain if you think any groups of people with this condition are particularly disadvantage Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or	

belief, sex, and sexual orientation or people with any other shared characteristics More information on how NICE deals with equalities issues can be found in the NICE equality scheme Find more general information about the Equality Act and equalities issues here.	
13. Are there any other issues that you would like the committee to consider?	

Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- Click or tap here to enter text.
- Click or tap here to enter text.
- Click or tap here to enter text.
- Click or tap here to enter text.
- Click or tap here to enter text.

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Single Technology Appraisal

Donanemab for treating mild cognitive impairment or mild dementia caused by Alzheimer's disease [ID6222]

Patient expert statement

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Patient expert statement

Part 1: Living with this condition or caring for a patient with Alzheimer's disease

Table 1 About you, Alzheimer's disease, current treatments and equality

1. Your name	Peter Almond
2. Are you (please tick all that apply)	☐ A patient with Alzheimer's disease? ☒ A patient with experience of the treatment being evaluated? ☐ A carer of a patient with Alzheimer's disease? ☐ A patient organisation employee or volunteer? ☐ Other (please specify):
3. Name of your nominating organisation	
4. Has your nominating organisation provided a submission? (please tick all options that apply)	☐ No (please review all the questions and provide answers when possible) ☒ Yes, my nominating organisation has provided a submission ☐ I agree with it and **do not wish to** complete a patient expert statement ☒ Yes, I authored / was a contributor to my nominating organisations submission ☐ I agree with it and **do not wish to** complete this statement ☒ I agree with it and **will be** completing
5. How did you gather the information included in your statement? (please tick all that apply)	☒ I am drawing from personal experience ☐ I have other relevant knowledge or experience (for example, I am drawing on others' experiences). Please specify what other experience: ☐ I have completed part 2 of the statement **after attending** the expert engagement teleconference

	☐ I have completed part 2 of the statement **but was not able to attend** the expert engagement teleconference ☒ I have not completed part 2 of the statement
6. What is your experience of living with Alzheimer's disease? **If you are a carer (for someone with Alzheimer's disease) please share your experience of caring for them**	I do not consider I have Alzheimer's disease. I consider that I have mild dementia which, without treatment, will result in Alzheimer's disease. But if you are asking about my current condition I can say that I feel 90% of my former self, ie able to think and act as I was, but with a touch more forgetfulness, a little more anxiety and disorganisation – and feeling my age a little more. The latter would probably be happening anyway, but I do seem to forget where I put my reading glasses a little more, I'm not focussed on reading books so much, and I tire more easily. Thankfully, I can drive as well as ever. I'm physically quite fit, ride my bike scores of miles (London to Brighton in two weeks (55 miles) and can hold my own in conversations on politics, military, potholes, women, TV, movies, dogs, you name it. And I've just spent the weekend up ladders trimming hedges, mowing lawns, digging weeds and moving large flower pots. Most of my family and friends do not believe I have mild dementia. But I and the medical people know I do.
7a. What do you think of the current treatments and care available for Alzheimer's disease on the NHS? **7b. How do your views on these current treatments compare to those of other people that you may be aware of?**	**I do not know anything about current treatments and care for Alzheimers in the NHS. I only know about my own trials experiences.** **Can't answer this. I drive from south surburban London to Re-Search Health's site in Guildford, Surrey, once a month for an infusion of donenamab (inside elbow), including every three months a psychological examination, three month visit to London for an MRI scan and a six month visit to Alliance in Kent for a PET scan.**
8. If there are disadvantages for patients of current NHS treatments for Alzheimer's disease (for example,	Can't answer this

how they are given or taken, side effects of treatment, and any others) please describe these	
9a. If there are advantages of donanemab over current treatments on the NHS please describe these. For example, the effect on your quality of life, your ability to continue work, education, self-care, and care for others? **9b. If you have stated more than one advantage, which one(s) do you consider to be the most important, and why?** **9c. Does donanemab help to overcome or address any of the listed disadvantages of current treatment that you have described in question 8? If so, please describe these** 9d. If you are able to comment on this, what would you consider to be a clinically meaningful benefit that you have seen (or would hope to see) with donanemab treatment? How would you recognise any benefit of treatment? For example, you might wish to consider particular symptoms of Alzheimer's disease getting better or not getting worse.	Can't answer this **I believe the donenemab I am currently taking is keeping me stable, or at least preventing me from becoming worse. The doctor who has been administering the drug to me every month for the past year – and before that a further 18 months either on donenamab or a placebo – has told me he thinks I am the same as I was when I started.** **For my brain not to deteriorate any further is, in my book, a decisive win.**
10. If there are disadvantages of donanemab over current treatments on the NHS please describe these. For example, are there any risks with donanemab? If you are concerned about any potential side effects you have heard about, please describe them and explain why	I am unable to discuss NHS treatments. As for side effects of donenamab I do not believe I have had any. No dizziness or brain bleeds anyway.
11. Are there any groups of patients who might benefit more from donanemab or any who may benefit less? If so, please describe them and explain why Consider, for example, if patients also have other health conditions (for example difficulties with mobility,	It might be more difficult to deliver donenamab to individuals whose veins are not quite so accessible, But sitting in a chair, or lying on a couch for 20 minutes for the infusion is not much of a hardship.

dexterity or cognitive impairments) that affect the suitability of different treatments	Those who do are in poor health condition may not take so well to regular infusions, even if only once a month. From my own experience I believe everyone with mild dementia would benefit from infusions of donenamab. Only those with full Alzheimers appear likely to be confused by the infusions.,
12. Are there any potential equality issues that should be taken into account when considering Alzheimer's disease and donanemab? Please explain if you think any groups of people with this condition are particularly disadvantage Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics More information on how NICE deals with equalities issues can be found in the NICE equality scheme Find more general information about the Equality Act and equalities issues here.	Disease and donenamab? I can only say that throughout Covid every member of my family went down with it – if only slightly for one or two. But I was not one of them. I stayed healthy throughout. Another amazing side effect of donenamab? Is it possible that some ethnic groups, such as black people with sickle cell anaemia, might have a stronger reaction to donenamab? Just thinking. I had some small experience of people with sickle cell in America in the 70s. But of course this was way before any thought of drugs to combat alzheimers.
13. Are there any other issues that you would like the committee to consider?	My donenamab trial ends this coming September. I have no idea what happens after that. My doctor has suggested I might return for check ups every three months, but so far visit No 41 is The End. Is there consideration for delivering the drug as a pill, or a liquid, to be taken orally? This would save much time and money for patients and staff. A visit to the chemist beats a trek to a local hospital.

	Can details of progress or stagnation of trials not be provided by the researchers to each individual? I believe radiologists have stopped looking for tau tangles in my brain (cleaned out?) or the continued presence of amyloids. What do I know?

Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

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External Assessment Group Report commissioned by the NIHR Evidence Synthesis Programme on behalf of NICE

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

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Produced by	**Southampton Health Technology Assessments Centre (SHTAC)**
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Declared competing interests of the authors and advisors

The authors declare none. Dr Jay Amin works as a sub-investigator for the Memory Assessment and Research Centre in Southampton. As part of this role, he undertakes consent, physical reviews and testing for people on trials for similar drugs to donanemab, including lecanemab (Eisai – CLARITY-AD) and aducanumab (Biogen – ENVISION). He has no personal interest in, or financial conflict with, any of these drugs. Dr Amin works in an NHS memory clinic at the Memory Assessment and Research Centre in Southampton. As part of this role, he recommends treatments for people with mild cognitive impairment and mild Alzheimer's disease. Therefore, he may be affected professionally by a change in

standard NHS practice as a result of this appraisal. Professor Perneczky has undertaken consultancy work and received occasional payments for participation in advisory boards and for speaker engagements. The advisory board and speaker engagements for Eli Lilly were not specifically about donanemab, but more generally about Alzheimer's diagnosis (early diagnosis and biomarkers in particular). Professor Perneczky has also advised Eisai and Novo Nordisk on the topic of Alzheimer's diagnosis in the last 12 months.

Rider on responsibility for report

The views expressed in this report are those of the authors and not necessarily those of the NIHR Evidence Synthesis Programme. Any errors are the responsibility of the authors.

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Contributions of authors

Ines Ribeiro critically appraised the health economic systematic review, critically appraised the economic evaluation, and drafted the report; Karen Pickett critically appraised the clinical effectiveness systematic review and drafted the report; Keith Cooper critically appraised the health economic systematic review, critically appraised the economic evaluation, and drafted the report; Joanne Lord coded aspects of the EAG analyses in the economic model, drafted the report and provided a quality assurance review of the cost-effectiveness chapters of the draft report; Joanna Picot critically appraised the clinical effectiveness systematic review, drafted the report and is the project co-ordinator and guarantor.

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LIST OF ABBREVIATIONS

AChEI	Acetylcholinesterase inhibitors
AD	Alzheimer's disease
ADAS-Cog13	13-Item Alzheimer's Disease Assessment Scale – Cognitive Subscale
ADCOMS	Alzheimer's Disease COMposite Score
ADCS-iADL	Alzheimer's Disease Cooperative Study – Activities of Daily Living Inventory
ADL	Activities of daily living
AE	Adverse event
APOE	Apolipoprotein E genotype
ARIA	Amyloid-related imaging abnormality
ARIA-E	Amyloid-related imaging abnormality of oedema/effusions
ARIA-H	Amyloid-related imaging abnormality of microhaemorrhages/hemosiderin deposits
Aβ	Beta-amyloid
BMI	Body mass index
BNF	British National Formulary
CDR-G	Clinical Dementia Rating Global Score
CDR-SB	Clinical Dementia Rating Sum of Boxes
CI	Confidence interval
CIC	Commercial in confidence
CL	Centiloid
CRD	Centre for Reviews and Dissemination
CS	Company submission
CSF	Cerebrospinal fluid
CSR	Clinical Study Report
CT	Computed tomography
DSU	Decision Support Unit
EAG	External Assessment Group
ECG	Electrocardiogram
EQ-5D-3L	European Quality of Life Working Group Health Status Measure 3 Dimensions, 3 Levels
EQ-5D-5L	European Quality of Life Working Group Health Status Measure 5 Dimensions, 5 Levels

FDG	Fluorodeoxyglucose
GPCOG	General Practitioner Assessment of Cognition
HRQoL	Health-related quality of life
HTA	Health technology assessment
iADRS	Integrated Alzheimer's Disease Rating Scale
ICER	Incremental cost-effectiveness ratio
IgG	Immunoglobulin G
ITT	Intention-to-treat
IV	Intravenous
LS	Least squares
LSM	Least-squares mean
MCI	Mild cognitive impairment
MCID	Minimal clinically important difference
mITT	Modified intention-to-treat
MMRM	Mixed-effect model for repeated measures
MMSE	Mini-Mental State Exam
MoCA	Montreal Cognitive Assessment
MRI	Magnetic resonance imaging
MWPC	Meaningful within-patient change
N/A	Not applicable
N3pG	N-terminal pyroglutamate modification of the third amino acid of Aβ
NCS	Natural cubic spline model
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NR	Not reported
PAS	Patient access scheme
PET	Positron emission tomography
PSA	Probabilistic sensitivity analysis
PSS	Personal social services
PSSRU	Personal Social Services Research Unit
Q4W	Every 4 weeks
QALY	Quality-adjusted life year
QoL	Quality of life
RCT	Randomised controlled trial
SAE	Serious adverse event

SD	Standard deviation
SE	Standard error
SLR	Systematic literature review
SmPC	Summary of product characteristics
STA	Single technology appraisal
SUVR	Standardised uptake value ratio
TA	Technology appraisal
TEAE	Treatment emergent adverse event
TSD	Technical Support Document
UK	United Kingdom

1 EXECUTIVE SUMMARY

This summary provides a brief overview of the key issues identified by the external assessment group (EAG) as being potentially important for decision making. It also includes the EAG's preferred assumptions and the resulting incremental cost-effectiveness ratios (ICERs).

Section 1.1 provides an overview of the key issues. Section 1.2 provides an overview of key model outcomes and the modelling assumptions that have the greatest effect on the ICER. Sections 1.3 to 1.6 explain the key issues in more detail. Background information on the condition, health technology, evidence and information on the issues are in the main EAG report.

All issues identified represent the EAG's view, not the opinion of the National Institute for Health and Care Excellence (NICE).

1.1 Overview of the EAG's key issues

Table 1 Summary of key issues

ID	Summary of issue	Report sections
1	Use of acetylcholinesterase inhibitors and memantine	2.3, 3.2.1.2 and 3.2.5.8.3
2	Choice of measure of cognition and function for use as the outcome measure of treatment effect in the economic model	3.2.2.1.1.6, 3.2.5, 4.2.9.1 and 6.3
3	Analysis of clinical effectiveness results for use in the economic model	3.2.5.3 and 3.2.6
4	Risk of bias associated with the TRAILBLAZER-ALZ trials and the potential impact on the measurement of the treatment effect	3.2.3 and 3.2.5.2
5	Impact of APOE ε4 allele status	3.2.5.8.1 and 3.2.5.9.2
6	Hazard ratios for mortality due to Alzheimer's disease	4.2.8
7	Assumptions on the duration of long-term treatment effect	4.2.9.2
8	Patient utility values for Alzheimer's disease health states	4.2.10.2.1
9	Caregiver utility values for Alzheimer's disease health states	4.2.10.2.2

The key differences between the company's preferred assumptions and the EAG's preferred assumptions are the estimates for the treatment duration of donanemab, the probabilities of moving to residential care and Alzheimer's disease mortality, the duration of the treatment

effect of donanemab, patient and caregiver utilities, and the estimates for diagnostic, monitoring and health state costs.

1.2 Overview of key model outcomes

NICE technology appraisals compare how much a new technology improves length (overall survival) and quality of life in a quality-adjusted life year (QALY). An ICER is the ratio of the extra cost for every QALY gained.

Following their response to the clarification questions, the company updated their economic model. The company's revised base case deterministic cost-effectiveness results are shown in Table 2 with a confidential PAS discount applied for donanemab. The ICER is £19,736 per QALY for donanemab versus BSC, with a QALY gain of 0.71 and an additional cost of £13,953.

Table 2 Company revised base case results with PAS for donanemab

Treatment	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER versus baseline (£/QALY)
Donanemab	[redacted]	1.76	£13,953	0.71	£19,736
BSC	[redacted]	1.05	-	-	-

Source: Partly reproduced from Table 27 of clarification response document and company's revised model ('Deterministic results' sheet).
BSC, best supportive care; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year.

1.3 The decision problem: summary of the EAG's key issues

No key issues were identified with respect to the decision problem.

1.4 The clinical effectiveness evidence: summary of the EAG's key issues

Issue 1 Use of acetylcholinesterase inhibitors and memantine

Report section	2.3, 3.2.1.2 and 3.2.5.8.3
Description of issue and why the EAG has identified it as important	The use of acetylcholinesterase inhibitors in people with MCI due to Alzheimer's disease and the use of memantine in people with either MCI or mild dementia due to Alzheimer's disease is outside the recommendations of NICE NG97. In the company's TRAILBLAZER-ALZ and TRAILBLAZER-ALZ 2 trials approximately 60% of participants received an acetylcholinesterase inhibitor or memantine. In response to clarification question A7 the company stated that at baseline in TRAILBLAZER-ALZ 2 45.2% of participants with MCI were

	on acetylcholinesterase inhibitor therapy and 13.4% were taking memantine. Although our clinical experts agreed that some people with MCI due to probable Alzheimer's disease would receive an acetylcholinesterase inhibitor off-label, neither of our experts stated that patients with MCI received memantine in clinical practice. We believe the use of acetylcholinesterase inhibitors and memantine in participants with MCI and the use of memantine for people with mild dementia due to Alzheimer's disease in the TRAILBLAZER-ALZ 2 RCT was higher than estimated in UK clinical practice.
What alternative approach has the EAG suggested?	We asked the company to provide iADRS and CDR-SB outcomes separately for the subgroup of people who did not receive pharmacological management in addition to donanemab (clarification question A1b). The company provided these results for the TRAILBLAZER-ALZ 2 trial and confirmed that iADRS and CDR-SB change from baseline outcomes were not significantly different for those who received acetylcholinesterase inhibitors or memantine at baseline and those who did not. This can be seen in CS Figures 11 and 12 which show these subgroup analyses for the iADRS and CDR-SB by baseline acetylcholinesterase inhibitor or memantine [labelled 'Medication use (No, Yes)' in the figures]. On the iADRS, there is a difference in the point estimates of the medication 'No' and 'Yes' subgroups but confidence intervals of the two subgroups are overlapping. On the CDR-SB measure the results for the two subgroups are very similar.
What is the expected effect on the cost-effectiveness estimates?	As the model uses the CDR-SB as the measure of treatment effect we would not expect an impact on cost-effectiveness estimates between the 'No' and 'Yes' medication subgroups.
What additional evidence or analyses might help to resolve this key issue?	Additional discussion with clinical experts on the degree to which acetylcholinesterase inhibitors or memantine are used off label for people with MCI due to probable Alzheimer's disease and the degree to which memantine is used off label for people with mild dementia due to probable Alzheimer's disease in clinical practice. Discussion about the potential impact of acetylcholinesterase inhibitors or memantine on measures of cognition and function in people with MCI or mild dementia due to probable Alzheimer's disease.

Issue 2 Choice of measure of cognition and function for use as the outcome measure of treatment effect in the economic model

Report section	3.2.2.1.1.6, 3.2.5, 4.2.9.1, and 6.3
Description of issue and why the EAG has identified it as important	EMA guidance published in 2018 on the clinical investigation of medicines for treating Alzheimer's disease states that there is no ideal tool for assessing the efficacy of treatments for dementia and considers a range of tools may be needed to assess treatment efficacy in a trial. The company's TRAILBLAZER-ALZ and TRAILBLAZER-ALZ 2 trials used five different measures (iADRS, CDR-SB, ADCS-iADL, ADAS Cog_{13} and MMSE) to measure cognition and/or function (disease progression). The iADRS was the primary

	outcome of both trials but CDR-SB from the TRAILBLAZER-ALZ 2 trial has been used as the measure of treatment effect in the economic model. On balance, we feel the use of the CDR-SB measure to inform the treatment effect in the company's economic model is appropriate, but we acknowledge that there is value in considering the iADRS as an alternative.
What alternative approach has the EAG suggested?	We requested (clarification question B5c) that the company provide the hazard ratio of progressing to clinically worse health states between donanemab and best supportive care for the iADRS measure and enable its use in the model.
What is the expected effect on the cost-effectiveness estimates?	The company tested the hazard ratio for disease progression based on the iADRS outcome from the TRAILBLAZER-ALZ 2 trial in response to clarification question B5c). This increases the ICER from the base case value of £19,736 to £34,074 per QALY. If the treatment effect for the model was based on data from the TRAILBLAZER-ALZ and TRAILBLAZER-ALZ 2 trials combined (see Issue 3), the impact of using either the CDR-SB or iADRS as the measure of treatment effect on the cost-effectiveness estimates is unknown. However, the results are likely to be less favourable to donanemab than presented in the company base-case analysis.
What additional evidence or analyses might help to resolve this key issue?	Additional expert clinical input regarding the most appropriate measure to capture treatment effect in the model. The measure used needs to be sensitive to changes in the cognition and function of people with MCI and mild dementia due to Alzheimer's disease and needs to be suitable for modelling Alzheimer's disease progression from MCI to severe Alzheimer's disease.

Issue 3 Analysis of clinical effectiveness results for use in the economic model

Report section	3.2.5.3 and 3.2.6
Description of issue and why the EAG has identified it as important	The company use a hazard ratio of disease progression (0.62, 95% CI 0.52 to 0.75) based on the CDR-SB outcome as a measure of treatment effect in the economic model that is estimated from the phase 3 TRAILBLAZER-ALZ 2 RCT only. In response to clarification question B5c the company have also provided a hazard ratio of disease progression based on the iADRS outcome from the TRAILBLAZER-ALZ 2 RCT (0.70, 95% CI 0.58 to 0.84). In the phase 2 TRAILBLAZER-ALZ trial the CDR-SB least squares mean change difference between the trial arms was smaller than for the TRAILBLAZER-ALZ 2 trial whereas the least squares mean difference in iADRS score was larger than for the TRAILBLAZER-ALZ 2 trial. The reasons for these differences are not easily explained. They could be a consequence of the slight differences in methodology of the trials and the differences in participant characteristics or they may be a consequence of the variability in the disease course between patients. We believe that, as the patients in both trials are representative of the patients who would

	receive donanemab in clinical practice, there should be the option to use data from both trials combined in the economic model.
What alternative approach has the EAG suggested?	We asked the company to conduct meta-analyses for the CDR-SB and iADRS outcomes and asked the company to add an option to use the results from the meta-analyses in the economic model (clarification question A18b and c). However, the company declined to do this stating that heterogeneity between the studies would limit the feasibility and validity of a meta-analysis.
What is the expected effect on the cost-effectiveness estimates?	Uncertain and likely to differ depending on which measure of treatment effect is used in the economic model. However, the EAG considers that the economic model results are likely to be less favourable to donanemab using the meta-analysis results for CDR-SB outcomes than in the company base-case analysis.
What additional evidence or analyses might help to resolve this key issue?	We would still like the company to provide a hazard ratio of disease progression that is based on data from both trials combined for the CDR-SB and iADRS outcomes.

Issue 4 Risk of bias associated with the TRAILBLAZER-ALZ trials and the potential impact on the measurement of the treatment effect

Report section	3.2.3 and 3.2.5.2
Description of issue and why the EAG has identified it as important	The EAG judged both the TRAILBLAZER-ALZ and TRAILBLAZER-ALZ 2 trials to be of an overall high risk of bias. We considered that the potential for participants and their supporters to become aware of participants' treatment allocation due to ARIA events and infusion-related reactions presented a high risk of bias that could affect the measurement of disease progression based on the CDR-SB in the trials, including the HR from the TRAILBLAZER-ALZ 2 trial that is used in the economic model. Additionally, we had some concerns about impact of risk of bias due to missing outcome data on these outcomes, as there were differences in reasons for participants discontinuing the trials between the trials' arms (e.g. adverse events).
What alternative approach has the EAG suggested?	We suggest that sensitivity analyses of the Cox proportional hazard model of disease progression as measured by the CDR-SB in which participants are censored after the first ARIA-E or infusion-related reaction event or both of these (if they have not already experienced disease progression) would be useful to explore the impact of potential unblinding on the treatment effect [redacted] We do not suggest additional analyses to explore the impact of attrition on the treatment effect. The company provided sensitivity analyses at the clarifications stage using missing at random and missing not at random assumptions.

What is the expected effect on the cost-effectiveness estimates?	The high risk of bias from potential unblinding means that the accuracy of the treatment effect used in the economic model (the HR of disease progression as measured by the CDR-SB) is uncertain. It is possible that the treatment effect may either be over- or under-estimated, which may change the cost-effectiveness estimates. The company's sensitivity analysis using the missing not at random assumption shows that the least-squares mean change difference between donanemab and placebo for disease progression based on the CDR-SB [redacted] in the primary analysis for the mITT population, suggesting some uncertainty in the magnitude of the treatment effect.
What additional evidence or analyses might help to resolve this key issue?	We would like the company to provide sensitivity analyses of the hazard ratio, using a Cox proportional hazard model, of disease progression over time to week 76 as measured by the CDR-SB in which participants who experience ARIA or infusion-related reactions or both are censored after the first occurrence (if they have not already experienced disease progression), for both the TRAILBLAZER-ALZ and TRAILBLAZER-ALZ 2 trials. We would also like the company to provide economic model scenario analyses using the hazard ratios for the treatment effect when these participants are censored. It would be desirable if the company also conducted the same sensitivity analyses of the hazard ratios with censoring of these participants when the iADRS is used to measure disease progression.

Issue 5 Impact of APOE ε4 allele status

Report section	3.2.5.8.1 and 3.2.5.9.2
Description of issue and why the EAG has identified it as important	Subgroup analyses of adverse events by APOE ε4 allele status indicate that this allele increases the risk of experiencing an ARIA event for people treated with donanemab. People who are homozygous for the APOE ε4 allele have a greater risk of experiencing ARIA events than people who are heterozygous for this allele and both subgroups have a greater risk than people who are not carriers of this allele. One of our clinical experts advised us that due to the risk of ARIA side effects in homozygous carriers of the APOE ε4 allele, these patients should probably not be treated with donanemab. That expert also commented that the potential risks and benefits of treatment would need to be clearly explained to heterozygous APOE ε4 carriers. Coupled to this, subgroup analyses of the iADRS and CDR-SB at 76 weeks from the TRAILBLAZER-ALZ 2 trial hint at potential differences in clinical response by APOE ε4 allele status. On both outcome measures the subgroup of people from TRAILBLAZER-ALZ 2 homozygous for the APOE ε4 allele showed a lower adjusted mean difference from placebo in disease progression than the subgroup heterozygous for this allele and both subgroups had a lower

	adjusted mean difference from placebo in disease progression than the subgroup of participants who were not carriers of the APOE ε4 allele. These results are subject to some uncertainty however as they are based on only the phase 3 TRAILBLAZER-ALZ 2 trial and, because of the smaller numbers in the homozygous subgroup, the 95% confidence interval for the central estimates are wider than for the other two subgroups.
What alternative approach has the EAG suggested?	We do not suggest an alternative approach. As the number of participants in TRAILBLAZER-ALZ 2 who were homozygous for the APOE ε4 allele is comparatively small (n=213 for the iADRS outcome, n=220 for the CDR-SB outcome) it may not be feasible to obtain a hazard ratio of disease progression for this subgroup that could be used in the economic model. The number of participants homozygous for the APOE ε4 allele could be increased if the data for TRAILBLAZER-ALZ were included, but at baseline only 53 participants in this RCT were identified as being homozygous for the APOE ε4 allele so numbers would still be relatively small and, any issues of heterogeneity between the trials would apply as they would for Key issue 3 above.
What is the expected effect on the cost-effectiveness estimates?	It is possible that cost-effectiveness may differ for different subgroups by APOE ε4 allele status, particularly for those homozygous for this allele. Even if effectiveness does not differ by APOE ε4 allele status, this subgroup is at a greater risk of experiencing ARIA events, but these events are already captured in the economic model.
What additional evidence or analyses might help to resolve this key issue?	Clinical expert opinion about their view of the balance between risks and benefits of donanemab treatment, particularly for people who are homozygous for the APOE ε4 allele. Clarification from the company about whether it would be possible to provide a hazard ratio of disease progression for the APOE ε4 homozygous subgroup that could be used in the economic model.

1.5 The cost-effectiveness evidence: summary of the EAG's key issues

Issue 6 Hazard ratios for mortality due to Alzheimer's disease

Report section	4.2.8
Description of issue and why the EAG has identified it as important	The company's model applies a single hazard ratio for mortality of 2.55 (relative to the general population mortality) for patients with mild, moderate and severe Alzheimer's disease dementia. The mortality for the general population was applied to patients with MCI due to Alzheimer's disease. Previous cost-effectiveness studies of donanemab, other published evidence and clinical expert opinion to the EAG suggest that the risk of death should increase with disease severity and therefore we consider that using a single hazard ratio for different health states may not be reflective of the evidence.

	In response to clarification question B17b, the company updated their model to include the option to vary the mortality hazard ratio according to the severity of Alzheimer's disease and provided hazard ratios from the NACC dataset to inform this new option. We do not consider the NACC hazard ratios to be plausible as these were higher for the mild than the moderate health state. The Crowell study reports hazard ratios for mortality for patients at age 80 years that seem a good approximation to the mortality for a population with a starting age of 73 years (the baseline age in the current model).
What alternative approach has the EAG suggested?	The EAG prefers to use mortality hazard ratios that increase with increasing disease severity. We use the mortality hazard ratios from the Crowell study for the 80-year-old subgroup in our base case. We explored the uncertainty around this by conducting alternative scenario analyses using different mortality hazard ratios from the literature.
What is the expected effect on the cost-effectiveness estimates?	Applying different hazard ratios for each disease stage from Crowell et al. leads to an increase in the ICER of £23,000 per QALY (from £19,736 to £42,736) for the company's base case.
What additional evidence or analyses might help to resolve this key issue?	Further clinical expert opinion on which are the most appropriate mortality hazard ratios to be used in the economic model.

Issue 7 Assumptions on the duration of long-term treatment effect

Report section	4.2.9.2
Description of issue and why the EAG has identified it as important	The company's model assumes that the full treatment effect of donanemab observed during the TRAILBLAZER-ALZ 2 trial period is retained for (a) 3.5 years after stopping treatment and then wanes to zero for the following five years (if patients stop after 18 months or due to amyloid clearance); (b) one year after stopping treatment and then wanes to zero for the following 2.5 years (if patients stop due to adverse events). The company's assumptions are based on two main arguments: the time taken to return to amyloid positivity (>24.1CL) after stopping treatment and the relation between amyloid clearance and clinical benefit. We acknowledge that the results from TRAILBLAZER-ALZ trial show that patients that discontinued treatment at six months due to amyloid clearance have not returned to amyloid positivity at 18 months, i.e., for one year. Also, there is trial evidence for amyloid targeting therapies which indicates a positive correlation between amyloid clearance and clinical efficacy measures, such as CDR-SB scores.

	However, we note that there is no evidence on the treatment effect beyond the trial period. The clinical experts advising the EAG consider the company's assumptions to be speculative due to lack of available evidence. The assumptions around the duration of the treatment effect have a considerable impact on the model results.
What alternative approach has the EAG suggested?	The EAG assumes that the full treatment effect is retained for a shorter period of one year after stopping treatment (based on trial evidence) and then wanes for the following 2.5 years (in line with the company's assumption that it takes around 3.5 years for patients to return to amyloid positivity) for patients discontinuing treatment after the fixed duration of 18 months, due to amyloid clearance or due to adverse events.
What is the expected effect on the cost-effectiveness estimates?	Applying the EAG preferred assumptions detailed above leads to an increase in the ICER of £25,530 per QALY (from £19,736 to £45,266) for the company's base case.
What additional evidence or analyses might help to resolve this key issue?	Further clinical expert opinion on the plausibility of the long-term treatment effect assumptions used in the economic model.

Issue 8 Patient utility values for Alzheimer's disease health states

Report section	4.2.10.2.1
Description of issue and why the EAG has identified it as important	The company's model uses patient's health state utility values assessed by caregivers using EQ-5D data obtained from the meta-analysis of Landeiro et al. 2020. The pooled estimates of patient utilities combine EQ-5D scores using different countries' value sets. The EAG notes that this is not in line with the NICE Reference Case which states that health state valuations should be derived from a representative sample of the UK population.
What alternative approach has the EAG suggested?	The EAG prefers to use EQ-5D scores using a UK value set and therefore we use the proxy-rated patient utilities from the GERAS study in our base case. The GERAS study reported proxy-rated EQ-5D patient utilities assessed by their caregivers for mild, moderate and severe health states. It includes patients from France (n=419), Germany (n=552) and the UK (n=526) but uses the UK value set to calculate patient utilities.
What is the expected effect on the cost-effectiveness estimates?	Using the patient utilities from the GERAS study leads to an increase in the ICER of £4,864 per QALY (from £19,736 to £24,601) for the company's base case.
What additional evidence or analyses might help to resolve this key issue?	Further discussion on which patient utility estimates are the most appropriate.

Issue 9 Caregiver utility values for Alzheimer's disease health states

Report section	4.2.10.2.2
Description of issue and why the EAG has identified it as important	The company conducted two vignette studies to derive caregiver utilities using the time trade-off approach, as they argued that the EQ-5D is not sensitive enough to measure the health-related quality of life of caregivers for patients with Alzheimer's disease. The utilities were reported by general population participants. We note that using time-trade-off utilities reported by general population participants does not meet the criteria for the NICE Reference Case. In our opinion, the company has not provided sufficient convincing evidence to support the use of a different method to derive utilities for use in the economic model.
What alternative approach has the EAG suggested?	The EAG prefers to use EQ-5D scores directly assessed by caregivers in our base case. The GERAS study reported EQ-5D utilities for the primary caregiver of patients with Alzheimer's disease living in the community setting in France, Germany and the UK. The EAG considers that the study utilities meet the NICE Reference Case. As the GERAS study utilities are higher than the utilities for the general population, we have made adjustments to the data used in the model by assuming that caregivers of patients with MCI and mild disease have the same quality of life as the general population based on the age and gender distribution of caregivers in the economic model. For the moderate and severe health states, we adjusted the general population utilities based on the relative decrement between health states observed in the GERAS study. We applied the same utilities regardless of the type of caregiver (spouse or child) and the setting where the patient lives (community or residential care). As the available evidence is not categorised that way, a lot of assumptions would be needed, which would add uncertainty to the results and we believe that this level of detail is unnecessary.
What is the expected effect on the cost-effectiveness estimates?	Using the general population utilities adjusted based on the GERAS study leads to an increase in the ICER of £17,986 per QALY (from £19,736 to £37,722) for the company's base case.
What additional evidence or analyses might help to resolve this key issue?	Further discussion on which caregiver utility estimates are the most appropriate.

1.6 Other issues: summary of the EAG's view

There are two other issues that we do not consider to be key issues, but which are worthy of consideration.

- What constitutes a clinically meaningful benefit? (Report sections 3.2.2.1.1.7 and 3.2.5). The goal of donanemab treatment is to [redacted]. In their submission the company consider a greater than 20% slowing of clinical progression to be a clinically meaningful benefit whereas a publication presenting the European consensus on disease-modifying trials in Alzheimer's disease states that a reduction in the rate of disease progression of 30% to 50% is a reasonable goal. The company also present time-based analyses and point out that this is an intuitive metric that can be readily understood. However, the company does not indicate what length of delay in disease progression they consider to be clinically meaningful and over what time frame this should occur. This is an important issue for clinicians, patients and their carers to understand when discussing the benefits and risk of treatment as part of the process of informed consent. We acknowledge that what clinicians, patients and caregivers feel is a clinically meaningful benefit may differ due to their different perspectives and that there are different ways to conceptualise clinically meaningful benefit in this disease area. We think discussion with clinicians, patients and carers to clarify their views on what constitutes a meaningful benefit of treatment would be helpful.
- We have raised and sought clinical expert opinion on a number of possible resource issues associated with the potential introduction of donanemab into the NHS (Report section 2.2.2.1). These include:
  - Amyloid positivity testing and monitoring of amyloid clearance
  - MRI scan resources
  - APOE ε4 testing
  - Memory clinic resources to deliver donanemab
  - Other resources issues (training)

1.7 Summary of EAG's preferred assumptions and resulting ICER

Based on the EAG's critique of the company's model (discussed in section 4), we have identified the following key aspects of the company base case with which we disagree. Our preferred model assumptions are the following:

1. **Treatment duration of donanemab**: No patients discontinue before 18 months due to reaching amyloid clearance.
2. **Risk of residential care**: Annual probabilities of moving to residential care from the GERAS study (see Table 32).

3. **Mortality risk for Alzheimer's disease**: Hazard ratios are assumed to increase with progression of disease and were taken from Crowell et al.[1] (see Table 33). **(Key issue)**
4. **Long-term treatment effect**: Full treatment effect retained for one year after stopping treatment and then waned for the following 2.5 years. **(Key issue)**
5. **Patient utility:** Use utility values from GERAS study, rather than Landeiro et al. (see Table 36). **(Key issue)**
6. **Caregiver disutility**: Caregiver utilities taken from the GERAS study, rather than the company's vignettes (see Table 37). **(Key issue)**
7. Number of caregivers per patient: Reduced from 1.8 to 1.
8. **Health care resource use:** Use health state costs from Wittenberg et al, which does not include unpaid care costs. We do not apply terminal care costs to avoid double counting (as these are included in the Wittenberg et al. estimates).
9. **Outpatient consultations:** We include an outpatient consultation for the diagnostic process and one consultation per model cycle for the first 18 months.

Table 3 shows the cumulative cost-effectiveness results of applying the EAG preferred model assumptions to the company's base case including the PAS discount for donanemab. Incorporating all the EAG assumptions, the ICER for donanemab vs BSC increases to £149,531 per QALY.

The change that has the most significant impact on the cost-effectiveness results is changing the assumptions for how long the treatment effect lasts, using an alternative source for the caregiver disutilities and the alternative mortality hazard ratios.

Table 3 Cumulative cost effectiveness results for the EAG's preferred assumptions with PAS for donanemab

Preferred assumption	Treatment	Total costs	Total QALYs	Cumulative ICER £/QALY
Company base-case	Donanemab	[redacted]	1.76	£19,736
	BSC	[redacted]	1.05	
+ No patients discontinue due to reaching amyloid clearance before 18 months	Donanemab	[redacted]	1.76	£20,291
	BSC	[redacted]	1.05	

Preferred assumption	Treatment	Total costs	Total QALYs	Cumulative ICER £/QALY
+ Full treatment effect for 1 year after stopping, then waned for the following 2.5 years	Donanemab	[redacted]	1.52	£46,113
	BSC	[redacted]	1.05	
+ Annual probabilities of moving to residential care from the GERAS study	Donanemab	[redacted]	1.81	£51,314
	BSC	[redacted]	1.37	
+ Mortality hazard ratios taken from Crowell 2023	Donanemab	[redacted]	1.95	£73,558
	BSC	[redacted]	1.53	
+ Patient utility from GERAS	Donanemab	[redacted]	2.20	£86,350
	BSC	[redacted]	1.84	
+ Caregiver disutility: GERAS	Donanemab	[redacted]	3.77	£134,039
	BSC	[redacted]	3.54	
+ One caregiver per patient	Donanemab	[redacted]	3.89	£137,775
	BSC	[redacted]	3.67	
+ Health care resource use does not include unpaid care costs	Donanemab	[redacted]	3.89	£145,894
	BSC	[redacted]	3.67	
+ Double counting of terminal care costs removed	Donanemab	[redacted]	3.89	£146,133
	BSC	[redacted]	3.67	
+ One outpatient consultation for diagnosis process and per model cycle up to 18 months	Donanemab	[redacted]	3.89	£149,531
	BSC	[redacted]	3.67	
EAG base case	Donanemab	[redacted]	3.89	£149,531
	BSC	[redacted]	3.67	

For further details of the exploratory and sensitivity analyses done by the EAG, these are shown in section 6.3.

2 INTRODUCTION AND BACKGROUND

2.1 Introduction

This report is a critique of the company's submission (CS) to NICE from Eli Lilly on the clinical effectiveness and cost effectiveness of donanemab for treating mild cognitive impairment (MCI) or mild dementia caused by Alzheimer's disease. It identifies the strengths and weakness of the CS. Two clinical experts were consulted to advise the external assessment group (EAG) and to help inform this report.

Clarification on some aspects of the CS was requested from the company by the EAG via NICE on 29 February 2024. A response from the company via NICE was received by the EAG on 15 March 2024 and this can be seen in the NICE committee papers for this appraisal.

2.2 Background

2.2.1 Background information on mild cognitive impairment or mild dementia caused by Alzheimer's disease

The company provide a clear overview of Alzheimer's disease, including its pathophysiology and epidemiology, risk factors, the diagnostic pathway, and the burden it places on people living with the condition and their caregivers, as well as its economic impact, in CS sections B.1.3.1, B.1.3.2 and B.1.3.3. The EAG have not identified any inaccuracies in the background information presented.

Below we provide an overview of MCI due to Alzheimer's disease and mild dementia due to Alzheimer's disease, the diagnostic pathway, including cognitive testing, the pathophysiology of Alzheimer's disease and the development of disease-modifying treatments, the significance of APOE ε4 gene carrier status in the condition and how the disease progresses over time. We supplement the background to the disease provided in the CS with additional information, including that provided by our clinical experts.

2.2.1.1 Overview of MCI and mild dementia due to Alzheimer's disease

As described in CS section B.1.3.1, Alzheimer's disease is a progressive neurodegenerative disease[2; 3] and it is the most common cause of dementia.[4; 5] Dementia is a clinical syndrome characterised by a decline in cognition that significantly impacts a person's abilities to function and carry out their daily tasks.[3; 6; 7] People living with dementia experience a deterioration in cognitive abilities such as memory, language, visuospatial and executive function, and may display changes in mood, behaviour and personality.[5; 8] The clinical

stages of Alzheimer's disease span from normal cognition, without any symptoms, to mild cognitive impairment (MCI; also referred to as the prodromal stage[9]) to dementia.[7] Progression through the stages typically occurs over a period of 15 to 25 years, and whilst the stages of Alzheimer's disease generally follow this continuum, there can be variation between individual patients.[7; 9] One of our clinical experts noted that some people, particularly those who are younger, can progress from normal cognition to severe Alzheimer's disease in as little as seven to eight years. As outlined in CS section B.1.3.1, dementia due to Alzheimer's disease can be categorised into three phases: mild or early stage, moderate stage, and severe or late-stage.[2] People living with MCI due to Alzheimer's disease or mild dementia due to Alzheimer's disease are the population of interest in this appraisal.

2.2.1.2 Diagnostic pathway and cognitive testing

CS Figure 3 outlines the dementia diagnosis pathway, which includes initial assessment by a general practitioner (GP) to exclude other factors as the cause of the problems the patient is experiencing. The figure states patients are then referred onward to a specialist memory assessment service if further investigation is required. We note from NICE NG97[10] that such services include memory clinics and community old age psychiatry, unless a person has suspected rapidly-progressive dementia, in which case it is recommended that they are referred to a neurological service.[10] CS Figure 3 shows that dementia is assessed through the use of tests of cognition and function, and neuropsychological testing and structural imaging may be undertaken to rule out other pathologies and to determine the dementia subtype a patient has. Both the EAG's clinical experts agreed with the company's depiction of the diagnostic pathway, with one expert noting that waiting lists for assessment are long. Both experts indicated that it is possible for patients to have two types of dementia concurrently (for example, Alzheimer's disease and cerebrovascular disease). One commented that this is commonly the case. Clinical expert advice to the EAG is that diagnostic decisions are often based on clinical assessment alone [and potentially also a brain computed tomography (CT) or magnetic resonance imaging [MRI] scan), with no further biomarker assessments [i.e. cerebrospinal fluid (CSF) testing or positron-emission Tomography (PET) scans] performed in most cases. One expert noted that this results in diagnostic uncertainty. Our experts informed us that blood-based biomarker tests for diagnostic testing in Alzheimer's disease are not yet currently available but are in development. One expert stated these are likely to be available within the next two to three years.

The CS outlines a range of cognitive tests that are available for assessing patients' mental and functional abilities (CS section B.1.3.1). In line with the information provided in the CS, the EAG's clinical experts indicated that the General Practitioner Assessment of Cognition (GPCOG) and the 6-item cognitive impairment test (6-CIT) are used in primary care for screening. The experts advised that the Mini-Mental State Examination (MMSE) or Montreal Cognitive Assessment (MoCA) in combination with the more detailed Addenbrooke's Cognitive Examination III (ACE IIII) assessment tool are used in memory clinics. One expert indicated that the MMSE is not used as much now as it used to be. Advice to us is that in clinical practice, after dementia has been diagnosed, progression is unlikely to be assessed. One clinical expert noted that a small proportion of patients who appear to be at high risk of progression to dementia may be offered a 1-year follow-up appointment. Our clinical experts agreed that most patients are discharged back into the care of their GP (with one noting that patients with mild AD dementia are typically started on a cholinesterase inhibitor and once they are stabilised on treatment, typically after about three months, they are discharged back to the care of their GP). We discuss the assessment of cognitive function in clinical practice and in the donanemab trials included in the CS further in section 3.2.2.1.1.

2.2.1.3 Amyloid beta peptide plaque pathology and the development of disease-modifying treatments for Alzheimer's disease

The central pathological features of Alzheimer's disease are amyloid beta peptide (Aβ) plaques and tau neurofibrillary tangles, which are proteins that form in the brain, neocortical structures and the medial temporal lobe.[2; 6] Aβ plaques have been identified in the brain up to two decades before people experience symptom onset.[5] The amyloid cascade hypothesis posits that these plaques are the earliest sign of the disease[5] and that accumulation of Aβ proteins is the central underlying agent in the pathology of Alzheimer's disease, with other features such as neurofibrillary tangles and dementia following on from this.[11] The EAG note that the amyloid cascade hypothesis is subject to some debate in the literature. For example, criticisms of the hypothesis include findings of a poor correlation between amyloid depositions in the brain and cognition, findings suggestive that Aβ may be neuroprotective, and a lack of clarity about the mechanism by which Aβ has a toxic impact on neurons.[11; 12]

As stated in CS section B.1.3.2, there are currently no disease-modifying treatments licenced in the UK for Alzheimer's disease that stop or moderate disease progression. Disease modifying treatments aim to alter the underlying pathology of the disease and thus aim to alter disease progression.[13] Currently, management of MCI due to Alzheimer's disease or mild dementia due to Alzheimer's disease focuses on improving symptoms. One of our clinical experts highlighted that there are no drugs licensed for MCI in the UK and the

licensed drugs for mild to moderate dementia due to Alzheimer's disease only have symptomatic effects (i.e. they improve symptoms, but do not delay symptom progression). Research into treatments for Alzheimer's disease has recently involved the development of disease-modifying drugs that target different amyloid forms and neurofibrillary tangles,[5] including donanemab which targets an epitope in brain amyloid plaques.[14]

As stated in the CS, the emergence of amyloid-targeting therapies, such as donanemab, will require the accurate identification of patients who are eligible for them; that is the identification of people who are amyloid positive (CS section B.1.3.1). The CS accurately states that among the prevalent population of people with a clinical suspicion of Alzheimer's disease approximately 100,000 people with MCI and approximately 62,000 people with mild dementia, are anticipated to be amyloid positive and thus be potentially eligible for an amyloid-targeting therapy (CS section B.1.3.1). The latter is based on a report by the NICE Decision Support Unit (DSU)[15] within a NICE HTA Innovation Laboratory Report on the potential issues that may arise in health technology assessment (HTA) assessments of new disease-modifying dementia treatments.[16] The EAG note that the DSU report states that these central estimates of current prevalence are subject to extensive uncertainty and also do not reflect the numbers of patients who would need to be screened or tested for these treatments. The DSU report estimates that a current prevalence of 283,000 people who will be eligible for amyloid testing.[15] Clinical expert advice to the EAG is that amyloid beta pathology is not currently typically confirmed in patients with probable Alzheimer's disease in clinical practice. PET scanning or CSF testing can be used to determine amyloid beta positivity.[16] We note that NICE NG97 currently only recommends testing for amyloid beta, using CSF testing, if this would help to determine the dementia subtype and knowing more about this would impact on clinical management.[10] As the company outline in the CS, NICE only recommend use of fluorodeoxyglucose-positron emission tomography-CT (FDG-PET) imaging for testing in dementia, and not amyloid-sensitive PET scanning[10] (CS section B.1.3.1).

Another potentially disease-modifying treatment for MCI due to Alzheimer's disease or mild dementia due to Alzheimer's disease, lecanemab, which is posited to work by binding to the Aβ soluble protofibrils,[17] is currently being appraised by NICE. Guidance is expected to be published in July 2024.[18]

2.2.1.4 APOE ε4 gene carrier status

There are a number of theorised causes of and risk factors for Alzheimer's disease, including genetic factors.[2] As mentioned in the CS, genetic factors include the presence of

the apolipoprotein E genotype e4 allele (APOE ε4),[2] which is substantially associated with a risk of developing Alzheimer's disease.[4; 7] We note that responses to Alzheimer's disease treatments have been found to be modified by whether or not patients are APOE ε4 carriers or non-carriers in clinical trials.[19] People can be either homozygous (two APOE ε4 alleles) or heterozygous (one APOE ε4 allele and one non-APOE ε4 allele) carriers of the APOE ε4 allele, with homozygotes having a greater risk of both developing Alzheimer's disease and developing it earlier in life.[20] Overall, around 15% to 25% of people have the APOE ε4 allele.[21] We were advised by one of our experts that around two thirds of patients with dementia due to Alzheimer's disease are heterozygous carriers.

We note that APOE ε4 carrier status is among the risk factors for adverse events of special interest associated with donanemab known as amyloid-related imaging abnormalities (ARIA) of oedema/effusion (ARIA-E) and of microhaemorrhages and hemosiderin deposits (ARIA-H) in the brain.[22] One expert advised us that the risk of severe side effects from donanemab is very high in homozygous carriers and due to this they would not treat these patients with donanemab. We discuss APOE ε4 carrier status and the risk of severe side effects from donanemab treatment, and testing patients for their carrier status, in more detail in sections 3.2.5.9 and 2.2.2.1.3, respectively.

2.2.1.5 Disease progression

As stated above, there is variation between individuals in how fast Alzheimer's disease develops and progresses. The total duration of Alzheimer's disease has been found to depend on age, sex, APOE ε4 genotype and baseline CSF tau.[9] Factors that are associated with a shorter disease period are male sex, abnormal CSF tau and APOE ε4 genotype, but the effects of these factors interact with the patient's disease stage.[9] One of our clinical experts noted that evidence of hippocampal/medial temporal lobe atrophy on structural brain imaging and evidence of neuropsychiatric symptoms were factors that affected progression of MCI to dementia.[23] The other felt the most important factor contributing to a more rapid decline (and therefore shorter disease duration) is vascular comorbidity. One study estimated that people with amyloid pathology or a clinical diagnosis of Alzheimer's disease-type dementia spend between two and 15 years in the preclinical stage, three to seven years in the MCI/prodromal stage, two to six years in the mild dementia stage and one to seven years in the moderate dementia stage[9] (the duration of the severe dementia stage was not examined in this study). We asked out two clinical experts to estimate how long patients typically remain in the severe dementia stage. One estimated 1-3 years, the other thought it was highly variable and estimated 1-10 years.

2.2.2 Background information on donanemab

Donanemab ([redacted]) is a humanised immunoglobin G1 (IgG) antibody, which targets and binds to the N-terminal pyroglutamate (N3pG) eipitope – a truncated form of Aβ. Through this mechanism, donanemab is thought to remove amyloid plaques from the brain (CS Table 2). The company applied for regulatory approval for donanemab in [redacted], with UK regulatory approval expected in [redacted] (CS Table 2). The company provided the donanemab draft Summary of Product Characteristics (SmPC) to the EAG via NICE during the appraisal. The draft SmPC states that donanemab is indicated [redacted]. The clinical experts advising the EAG expect symptomatic and nonmedication treatments to be used alongside donanemab in clinical practice.

Donanemab is administered via intravenous infusion (CS Table 2) over a period of at least 30 minutes. The [redacted] dose is 700 mg every four weeks for the first three doses, after which a dose of 1,400 mg every four weeks is administered. The [redacted] treatment should be continued until amyloid plaques are cleared (as confirmed by a validated test) for up to a maximum period of 18 months. Alternatively, treatment should be continued for up to 18 months if amyloid plaque clearance cannot be monitored using a validated method. After patients have received an infusion, [redacted] they should be observed for at least 30 minutes.

The draft SmPC outlines that [redacted]. The draft SmPC also indicates that [redacted]

Neither of our clinical experts thought that it was likely that patients would be considered for retreatment with donanemab (it would be the exception). Both thought patients would have progressed to moderate dementia by the time amyloid had reaccumulated and would therefore be out of scope for donanemab treatment.

2.2.2.1 Resources to deliver donanemab

The potential introduction of donanemab into the NHS raises a number of possible resource issues, including the need to test for amyloid positivity at the start of treatment and amyloid clearance during treatment, the use of MRI scans for monitoring ARIA events, the need to test patients to establish their APOE ε4 status, and a current lack of resources in memory clinics to deliver the treatment. We provide an overview of these and other issues in this section. Please see section 4.2.11 for a detailed critique of the company's resource use assumptions in their economic model.

2.2.2.1.1 Amyloid positivity testing and monitoring of amyloid clearance

As stated in section 2.2.1.3, clinical expert advice to the EAG is that amyloid beta pathology is not currently typically confirmed in patients in clinical practice. CS Table 2 acknowledges that this will be an additional test that will be needed prior to patients having treatment, if donanemab is approved for use in the NHS. As stated in section 2.2.1.3, CS section B.1.3.1 outlines that PET scanning and CSF tests can be used to establish amyloid positivity. The CS states that there are currently three amyloid-PET tracers that have been approved by the MHRA for use in the UK. These are florbetapir (Amyvid), flutemetamol (VIZAMYL) and florbetaben (Neuraceq). All these tests are indicated for people undergoing assessment for Alzheimer's disease or other causes of cognitive impairment. However, the CS acknowledges that there is currently limited access to PET scanning in the NHS. Given this and other considerations (e.g. cost), the company state that clinicians advised them that demand for CSF testing for the presence of amyloid plaques is likely to increase. One of our experts advised us that currently fewer than 5% of patients undergo CSF testing.

The CS states that 10-15% of patients would not be suitable for CSF testing (CS section B.1.3.1) and our experts agreed with this. The experts advised that some patients cannot undergo this due to factors such as being immunocompromised, having increased intra-cranial pressure, anticoagulant drug use or because of anatomic characteristics (e.g. spinal scoliosis). One of our clinical experts thought that CSF testing would be acceptable to patients, stating it is safe and patient discomfort is minimal. Our other expert thought that some patients would not want to undergo a lumbar puncture.

Clinical expert advice to us is that PET scanning would be suitable for most patients (one estimated that no more than 5% of patients would be unsuitable for this).

As outlined above, [redacted] donanemab treatment ceases when amyloid plaques have cleared (when plaque monitoring with a validated method is possible) up to a period of 18 months or continues for 18 months if monitoring with a validated test is not possible. Clinical expert advice to the EAG is that given the current lack of availability of PET scans in the NHS, it is likely patients will not receive follow-up scans and most patients will therefore continue treatment to month 18, unless they stop earlier due to side effects such as ARIA. CS section B.1.3.1 notes that [redacted].

2.2.2.1.2 MRI scan resources

The potential introduction of donanemab into the NHS would also increase the need for MRI scans to be performed, [redacted]. The NICE HTA Innovation Laboratory Report on potential issues in evaluating disease-modifying treatments for dementia notes that ARIA adverse events necessitate additional MRI tests for close monitoring of this adverse event.[16] One clinical expert advised the EAG is that there are unlikely to be enough MRI scanners available in the NHS. Furthermore, they stated that there is a lack of radiologists available with the expertise needed to diagnose ARIA. The other expert commented that it can take weeks or months to receive an MRI report, so there would need to be a mechanism in place for timely feedback if ARIA events occur so that treatment can be suspended or stopped. We therefore note that MRI use, availability, expertise and the speed at which results can be made available are other resource considerations associated with the potential introduction donanemab into the NHS.

2.2.2.1.3 APOE ε4 testing

The company assume in their economic model that everyone who is eligible to receive donanemab will require an APOE ε4 test before treatment commences (CS Table 38). Our experts agreed that this test will be needed in every patient because this will aid an informed discussion of the risks versus the benefits of treatment (the risk/benefit profile may differ by APOE status). CS Table 2, which summarises the administration requirements associated with donanemab, does not list this as an additional test or investigation. The NICE HTA Innovation Laboratory Report[16] and one of our experts noted that this test is not currently routinely carried out in the NHS.

2.2.2.1.4 Memory clinic resources to deliver donanemab

It was also noted by one of our experts that memory clinics tend to be in city centres or community hospitals and that these settings do not have the resources, in terms of skills and equipment (such as resuscitation equipment), to be able to deliver an intravenous drug such as donanemab. Additionally, most memory clinics do not perform CSF tests. The settings that our clinical experts suggested would be suitable locations for the administration of donanemab were an acute general hospital (e.g. within a day assessment unit or infusion centre) or in a tertiary research centre.

2.2.2.1.5 Other resource issues

One of our experts highlighted that memory clinic clinicians will need training on the interpretation of CSF/PET amyloid results and of APOE ε4 genotype results. They commented that delivery of the drug would not only need a hospital setting, but also appropriately-trained staff to deliver it.

2.2.3 The position of donanemab in the treatment pathway

Due to a lack of pharmacological treatment options for MCI to date, an MCI treatment pathway has yet to be established. However, a very recent discussion paper from NHS England 'Dementia programme and preparation for new Alzheimer's disease modifying treatments'[24] (last updated 1 February 2024) includes a diagram showing the likely position of new medicines for Alzheimer's disease which accords with the company's proposed positioning of donanemab (CS B.1.3.4). We have created a version of the diagram which shows first-line therapy only and where donanemab is positioned for MCI and mild Alzheimer's disease (shown in yellow in Figure 1). In the mild Alzheimer's disease population donanemab is anticipated to be used alongside the acetylcholinesterase inhibitor monotherapies (donepezil, galantamine or rivastigmine) which are recommended as options in the NICE guideline NG97[10] for managing mild to moderate Alzheimer's disease. For people with moderate Alzheimer's disease who are intolerant of or who have a contraindication to acetylcholinesterase inhibitors, memantine monotherapy is a recommended option. Additionally, people with moderate Alzheimer's disease or severe Alzheimer's disease who are already taking an acetylcholinesterase inhibitor can be offered memantine in addition. However, as donanemab is expected to be indicated for the management of MCI due to Alzheimer's disease or mild Alzheimer's disease dementia (not moderate dementia) we would not expect donanemab to be used alongside memantine.

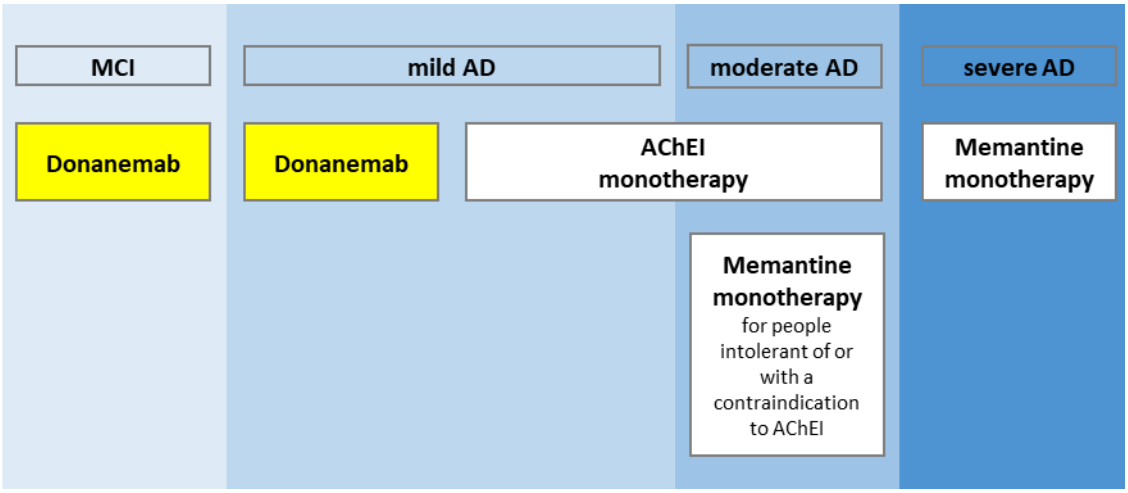

Figure 1 First-line therapies[a] for mild cognitive impairment and Alzheimer's disease at different severity levels.

Source: Figure based partly on a diagram presented in Annex A of the NHS England discussion paper 'Dementia programme and preparation for new Alzheimer's disease modifying treatments'[24]
AChEI, acetylcholinesterase inhibitor; AD, Alzheimer's disease; MCI, mild cognitive impairment.
[a] For people with an established diagnosis of Alzheimer's disease who have moderate or severe disease and who are already in receipt of AChEI therapy can be offered memantine in addition to the AChEI.

The company state that the acetylcholinesterase inhibitors and memantine may be used earlier in the treatment pathway than shown in Figure 1 and as recommended in the NICE guideline NG97.[10] The company report results from an Adelphi Real World Alzheimer's disease disease-specific programme (DSP) cross-sectional survey which found [redacted] MCI patients used off-label acetylcholinesterase inhibitors and [redacted] patients with mild AD dementia used acetylcholinesterase inhibitors. From the information provided in response to clarification question A4 we believe the Adelphi survey was [redacted] Although not explicitly stated in the CS or in response to clarification question A4 we believe that the data presented are [redacted] Our two clinical experts agreed that acetylcholinesterase inhibitors are used off-label in people with MCI due to probable Alzheimer's disease and that the proportion of people receiving acetylcholinesterase inhibitors identified by the company's Adelphi survey seemed realistic, although one clinical expert's experience was that less than 20% of people with MCI due to probable Alzheimer's disease would receive an acetylcholinesterase inhibitor off-label.

All people with MCI or mild dementia are expected to receive non-pharmacological therapy and support appropriate to their needs. CS B.1.3.4 lists social support, assistance with day-to-day activities, information and education, community dementia teams, home nursing and personal care, community services e.g. meals-on-wheels, befriending services, day centres,

respite care and care homes. Our clinical experts noted that some of the listed options, (e.g. care homes) would be more relevant for people with more advanced dementia.

People caring for those with MCI or mild dementia may obtain support from some of the above services and carer support groups.

EAG comment

The company submission provides a clear and accurate overview of Alzheimer's disease. We have supplemented the company's information with additional details on some areas we believe may be important for the decision-making process in this appraisal and insights provided by our clinical experts.

2.3 Critique of the company's definition of the decision problem

Table 4 summarises the decision problem addressed by the company in the CS in relation to the final scope issued by NICE and the EAG's comments on this. The company's decision problem deviates from the NICE scope with respect to the comparator therapy that people with MCI receive. The NICE scope specifies the single comparator of non-pharmacological management for people with MCI whereas in the company's decision problem there are two comparators for people with MCI, either non-pharmacological management alone (as per the NICE scope) or non-pharmacological management with symptomatic treatment for Alzheimer's disease (an acetylcholinesterase inhibitor or memantine). The company decision problem is aligned with the population in the company's clinical trials, and although we note that treatment with an acetylcholinesterase inhibitor or memantine is not recommended for people with MCI in NICE guidance, our clinical experts agree that acetylcholinesterase inhibitors are currently being used by a small proportion of people with MCI due to probable Alzheimer's disease (one expert estimated that <10% to 20% of participants may be in receipt of these). We discuss this further in section 3.2.1.2 of this report and raise this is a key issue (Key Issue 1).

Table 4 Summary of the decision problem

	Final scope issued by NICE	Company's decision problem	Rationale if different from the final NICE scope	EAG comments
Population	People with MCI or mild dementia due to AD	As per final scope	N/A	Neither the scope nor the company's decision problem specifies which neuro-psychological test should be used to measure disease severity. We note the company states in CS B.2.3.1 that no single test is recognised as the gold standard. To be

	Final scope issued by NICE	Company's decision problem	Rationale if different from the final NICE scope	EAG comments
				enrolled in the company's two pivotal trials, TRAILBLAZER-ALZ and TRAILBLAZER-ALZ 2, trials participants had to have an MMSE score of 20 to 28 inclusive which our clinical experts believed would be representative of the typical NHS population with MCI or mild dementia.
Intervention	Donanemab with or without symptomatic treatments for AD	As per final scope	N/A	The intervention matches that described in the final scope and draft SmPC. Both our clinical experts expected donanemab to be administered in combination with symptomatic and non-medication treatments in clinical practice.

	Final scope issued by NICE	Company's decision problem	Rationale if different from the final NICE scope	EAG comments

Comparators	Established clinical management without donanemab, including but not limited to:
	• For MCI due to AD
	  • Non-pharmacological management
	• For mild dementia due to AD
	  • Non-pharmacological management with or without symptomatic treatment for AD (an acetylcholinesterase inhibitor [AChEI])
		Patients were permitted symptomatic treatment with AChEIs or memantine, so established clinical management without donanemab both for MCI due to AD and mild dementia due to AD included: Non-pharmacological management with or without symptomatic treatment for AD (an AChEI or memantine)	N/A	For people with MCI the scope specifies a single comparator of non-pharmacological management. In contrast, the company's decision problem permits patients with MCI to receive either non-pharmacological therapy alone or in combination with an AChEI or memantine.

Outcomes	The outcome measures to be considered include: • cognitive and functional impairment • non-cognitive symptoms (e.g. behavioural and psychiatric symptoms) • mortality • ability to remain independent • admission to full-time care • adverse effects of treatment	The outcome measures addressed in the decision problem generally align with the final scope, with some minor differences. The	Data on admission to full time care and non-cognitive symptoms were not directly	The NICE scope did not specify which measures of cognition and function should be included and the company reports results for the

	Final scope issued by NICE	Company's decision problem	Rationale if different from the final NICE scope	EAG comments

	• health-related quality of life	outcome measures address in the submission are as follows:
		• Measures of cognition and function:
		  • iADRS change from baseline *(primary endpoint)*
		  • CDR-SB change from baseline
		  • ADCS-iADL change from baseline
		  • ADAS-Cog_{13} change from baseline
		  • MMSE change from baseline
			collected during the trial and as such are not available to present. The timeframe of the trial was too short to collect information on full time care, especially given that the patient cohort is in early stages of the disease.	change from baseline in five different measures. Three outcomes in the scope are not included in the decision problem because they were not reported in the trials (non-cognitive symptoms, ability to remain independent, admission to full-time care). The company includes three biomarker-related endpoints and time-based analyses of disease progression which were not included in the NICE scope. We discuss the outcome measures in more

	Final scope issued by NICE	Company's decision problem	Rationale if different from the final NICE scope	EAG comments

		• Biomarker-related endpoints:
		  • Change in amyloid plaque deposition from baseline as measured by florbetapir F18 PET scan
		  • Change in brain tau deposition from baseline as measured by flortaucipir F18 PET scan
		  • Change in volumetric magnetic resonance imaging (vMRI)
				detail in section 3.2.2.

	Final scope issued by NICE	Company's decision problem	Rationale if different from the final NICE scope	EAG comments

		measures from baseline
		• Time-based analyses of disease progression measured with:
		  • CDR-G
		  • CDR-SB
		• Health-related quality of life:
		  • QoL-AD
		• Adverse effects of treatment		

Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from a National Health Service (NHS) and Personal Social Services (PSS) perspective. The use of donanemab is conditional on the presence of amyloid pathology. The economic modelling should include the costs associated with diagnostic testing for amyloid pathology in people with AD who would not otherwise have been tested. A sensitivity analysis should be provided without the cost of the diagnostic test. See section 4.8 of the guidance	The base case is aligned with the NICE reference case. Additional scenario analyses examining societal costs were also explored.	Caregiver informal care costs were explored in scenario analyses, in line with the following NICE guidance from the NICE health technology evaluations manual:	The company's cost-utility analysis adheres to the NICE reference case except for the estimation of utilities and health care costs (see section 4.2.1). CS Table 2 states that a simple PAS discount has been submitted. The company apply the PAS price in the

	Final scope issued by NICE	Company's decision problem	Rationale if different from the final NICE scope	EAG comments
	development manual (available here: https://www.nice.org.uk/process/pmg36/chapter/introduction-to-health-technology-evaluation)		4.4.24. When care by family members, friends or a partner might otherwise have been provided by the NHS or PSS, it may be appropriate to consider the cost of the time of providing this care, even when adopting an NHS or PSS perspective[25]	economic evaluation (see section 5.1).
Subgroups	If the evidence allows the following subgroups will be considered: Apolipoprotein E 4 (ApOE-4) gene carrier status MCI due to AD Mild dementia due to AD	The data presented in this submission are not presented in the subgroups outlined in the final scope. The proportion of patients entering the model in the MCI due to AD and Mild dementia due to AD health states	The study was not powered to detect a difference in these groups and subgroup analyses suggest that these are not treatment effect modifiers.	No cost-effectiveness evidence is presented for the subgroups in the NICE scope, aside from exploring the impact of differing proportions of AD patients entering the model in the MCI and mild

	Final scope issued by NICE	Company's decision problem	Rationale if different from the final NICE scope	EAG comments
		will however be explored in scenario analyses.		dementia health states. CS section B.2.6.7 presents clinical effectiveness evidence for subgroups by baseline characteristics for the iADRS and CDR-SB outcomes, including ApOE-4 genotype and the Alzheimer's disease clinical stages of MCI and mild dementia. CS Appendix C presents clinical effectiveness evidence for a low-medium tau population (including analyses by baseline characteristics in this subgroup).

	Final scope issued by NICE	Company's decision problem	Rationale if different from the final NICE scope	EAG comments
Special considerations including issues related to equity or equality	No equality issues have been identified	As per final scope	N/A	The EAG is not aware of any equity or equality considerations that have not already been considered by the NICE equality impact assessment – Scoping.[26]

Source: CS Table 1 with the addition of EAG comments in the final column
AChEI, acetylcholinesterase inhibitor; AD, Alzheimer's disease; ADAS-Cog13, 13-Item Alzheimer's Disease Assessment Scale – Cognitive Subscale; ADCS-iADL, Alzheimer's Disease Cooperative Study – Activities of Daily Living Inventory; CDR-G, Clinical Dementia Rating – Global Score; CDR-SB, Clinical Dementia Rating – Sum of Boxes; CS, company submission; EAG, External Assessment Group; iADRS, Integrated Alzheimer's Disease Rating Scale; MCI, mild cognitive impairment; MMSE, Mini-Mental State Exam; N/A, not applicable; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; PAS, Patient Access Scheme; PET, positron emission tomography; PSS, personal social services; QoL-AD, Quality of Life in AD; SmPC, Summary of Product Characteristics; vMRI, volumetric MRI

3 CLINICAL EFFECTIVENESS

3.1 Critique of the methods of review(s)

The company conducted a systematic literature review (SLR) to identify studies on the clinical efficacy and safety of disease-modifying therapies, including donanemab, for early symptomatic Alzheimer's disease (CS Appendix B, sections B.1 and B.1.1.1). As the review included studies of other disease-modifying treatments, the eligibility criteria were wider than the company's decision problem specified in CS Table 1, but we note that the criteria would have captured relevant studies of donanemab. The searches for the review were conducted in June 2023 and updated in August 2023 (CS Appendix B, sections B.1 and B.1.2.1). The EAG have not identified any key concerns with how the review was conducted and we believe it is unlikely that relevant studies will have been missed. Our detailed critique of the company's review can be found in Appendix 1.

3.2 Critique of studies of the technology of interest, the company's analysis and interpretation (and any standard meta-analyses of these)

3.2.1 Included studies

The company's systematic literature review identified three randomised controlled trials (RCTs) providing evidence for the clinical efficacy and safety for donanemab in a population of patients with MCI due to Alzheimer's disease or with mild dementia due to Alzheimer's disease: TRAILBLAZER-ALZ, TRAILBLAZER-ALZ 2 and TRAILBLAZER-ALZ 4. The key features and role of these RCTs in this technology appraisal are summarised in Table 5.
As Table 5 states, only the phase 3 TRAILBLAZER-ALZ 2 RCT contributes clinical effectiveness data to the economic model. Six clinical outcomes from the trial are used in the company's economic model:

- The hazard ratio of disease progression based on the CDR-SB measurement scale (with a scenario analysis based on the iADRS).
- Four adverse events:
  - Amyloid-related imaging abnormality (ARIA) events
  - Injection related reactions
  - Hypersensitivity
  - Anaphylactic reactions
- A mortality risk associated with donanemab treatment

We believe that the economic model should include the option to draw on the combined clinical effectiveness data from the phase 2 TRAILBLAZER-ALZ and the phase 3 TRAILBLAZER-ALZ 2 RCTs. Consequently, we present the study and patient

characteristics of both these trials alongside each other in sections 3.2.1.1 and 3.2.1.2 respectively. The definition of the trial outcomes is discussed in section 3.2.2.

We do not critique the TRAILBLAZER-ALZ 4 head-to-head study of donanemab versus aducanumab in people with early symptomatic Alzheimer's disease as this is out of scope. However, we do critique the results from the integrated safety set which includes data from the patients in TRAILBLAZER ALZ 4 who received donanemab (section 3.2.5.9).

Table 5 Summary of sources of clinical effectiveness evidence

	TRAILBLAZER-ALZ (NCT03367403)	**TRAILBLAZER-ALZ 2 (NCT04437511)**	**TRAILBLAZER-ALZ 4 (NCT05108922)**
Trial type	Placebo controlled phase 2 trial of donanemab.	Placebo controlled phase 3 trial of donanemab.	Head-to-head phase 3 trial (donanemab vs aducanumab).
Trial funding	Eli Lilly and Company	Eli Lilly and Company	Eli Lilly and Company
Patient group	MCI due to AD or Mild AD dementia MMSE score 20 to 28 (inclusive) Quantitative tau levels below a specific upper threshold defined by a tau PET SUVR of >1.46.	MCI due to AD or Mild AD dementia MMSE score 20 to 28 (inclusive) No upper limit for quantitative tau levels.	Early symptomatic AD MMSE score 20 to 30 (inclusive) CDR-G score of 0.5 or 1 No upper limit for quantitative tau levels.
Role of clinical-effectiveness results in this submission	Results presented in CS Appendix 1.1 Does not inform cost-effectiveness analyses.	Results presented in CS section B.2.6. Informs cost-effectiveness analyses.	Results not relevant to submission.
Role of safety results in this submission (CS section B.2.10)	Included in the integrated safety dataset.	Safety data presented separately as well as also being included in the integrated safety dataset	Included in the integrated safety dataset.

Source: EAG created table
AD, Alzheimer's disease; CDR-G, Clinical Dementia Rating Global Score; CS, company submission; MCI, mild cognitive impairment; MMSE, Mini-Mental State Exam; PET, positron emission tomography; SUVR, standardised uptake value ratio.

3.2.1.1 Study characteristics

TRAILBLAZER-ALZ and TRAILBLAZER-ALZ 2 are the company-sponsored, multi-centre, double-blind phase 2 and phase 3 RCTs (respectively) of donanemab versus placebo. The

study design of TRAILBLAZER-ALZ 2 is shown in CS Figure 5, a corresponding figure for TRAILBLAZER-ALZ is not provided but the study is described in the published paper[27] and the EAG also had access to the Clinical Study Reports (CSRs) of both RCTs. To allow comparison between TRAILBLAZER-ALZ and TRAILBLAZER-ALZ 2 we have summarised the study designs in Table 6.

In both trials the dose of donanemab was as is expected to be used in clinical practice, (as described in CS Table 2) for a double-blind period of 76 weeks. Measurement of amyloid plaque reduction by PET occurred at the same timepoints during the double-blind period with TRAILBLAZER-ALZ having an additional measurement in the case of early discontinuation. In both trials during the double-blind period the result of the PET scans could signal treatment step-down (TRAILBLAZER-ALZ only) or treatment completion (both trials, patients were switched to placebo) (Table 6).

Participants in the TRAILBLAZER-ALZ 2 RCT were stratified by tau pathology (low-medium versus high) which was not relevant in the TRAILBLAZER-ALZ study because people with high tau were not eligible to be enrolled in the trial (Table 7). We note that the company does not anticipate that tau pathology will need to be identified to determine whether a patient is eligible for donanemab treatment in clinical practice (CS Appendix C.1.1). Randomisation was not stratified by receipt of symptomatic treatment for dementia which the EMA Guideline on the clinical investigation of medicines for the treatment of Alzheimer's disease[28]} states should be done for investigations into disease modifying treatments.

Table 6 Comparison of TRAILBLAZER-ALZ and TRAILBLAZER-ALZ 2 study designs

	TRAILBLAZER-ALZ (Phase 2 RCT)	**TRAILBLAZER-ALZ 2 (Phase 3 RCT)**
Intervention	Donanemab: 700 mg IV Q4W for first 3 doses and then 1400 mg IV Q4W.	Donanemab: 700 mg IV Q4W for first 3 doses and then 1400 mg IV Q4W.
Comparator	Placebo IV Q4W	Placebo IV Q4W
Randomisation ratio	1:1	1:1
Randomisation stratified by	Investigative site	Investigative site Tau pathology (low-medium versus high)
Length of double-blind period	76 weeks[a]	76 weeks
Length of extension period	No extension period[b]	78 weeks
Measurement of amyloid plaque reduction during the double-blind period[c]	Week 24 Week 52 Week 76 Or at early discontinuation	Week 24 Week 52 Week 76

	TRAILBLAZER-ALZ (Phase 2 RCT)	TRAILBLAZER-ALZ 2 (Phase 3 RCT)
Amyloid plaque level (assessed by florbetapir PET) that signalled treatment step-down or treatment completion	Donanemab arm could receive 700mg dose if amyloid plaque level: <25 but ≥11 Centiloids Donanemab arm could switch to placebo if amyloid plaque level: <11 Centiloids on any single PET scan or <25 but ≥11 Centiloids on 2 consecutive PET scans	Donanemab arm could complete treatment and receive placebo if amyloid plaque level: <11 Centiloids on any single PET scan or <25 but ≥11 Centiloids on 2 consecutive PET scans
Timing of ARIA monitoring by MRIs	Week 4 Week 12 Week16 Week 24 Week 36 Week 52 Week 76 Unscheduled MRIs at investigator discretion	Week 4 Week 12 Week 24 Week 52 Week 76 Unscheduled MRIs at investigator discretion.
Frequency of imaging if ARIAs detected	Every 4 to 6 weeks until resolution or stabilisation.	Every 4 to 6 weeks until resolution or stabilisation.
Final efficacy and adverse events assessments	Week 76	Week 76
Treatment assignments in extension period	No extension period	Participants randomised to donanemab in the double-blind period either: - continued to receive donanemab if they did not meet the treatment completion criteria[d] at week 76 (visit 21) Or - received placebo starting at visit 22 (week 78) if they did meet the treatment completion criteria[d] by week 76 (visit 21). Participants randomised to placebo in the double-blind period received donanemab starting at visit 22[e]
Maximum duration of treatment	72 weeks	150 weeks[f]

Source: CS Section B.2.3.2, Mintun et. el.[27] including trial protocol, TRAILBLAZER-ALZ CSR,[29] Sims et. al.[30] and TRAILBLAZER-ALZ 2 CSR.[31]
ARIA, amyloid-related imaging abnormality; CSR, Clinical Study Report; IV, intraveneous; mg, milligrams; MRI, magnetic resonance imaging; PET, positron emission tomography; Q4W, every 4 weeks; RCT, randomised controlled trial
[a] Donanemab treatment given for up to 72 weeks with the final efficacy and safety assessments occurring four weeks after the last infusion at 76 weeks.

[b] There was an immunogenicity and safety follow-up period. The length of this is stated as 36 weeks in the trial protocol but [redacted] weeks in the CSR. This follow-up is part of the TRAILBLAZER-LTE (Part B) safety follow-up (referred to in CS B.2.10) and TRAILBLAZER-EXT[32] trials.
[c] amyloid plaque reduction was measured by florbetapir F18 PET scans
[d] <11 Centiloids on any single PET scan or <25 but ≥11 Centiloids on 2 consecutive PET scans.
[e] These participants followed the same dose titration as the donanemab participants in the double-blind period of the trial (i.e. 700 mg IV Q4W for first 3 doses and then 1400 mg IV Q4W).
[f] CS states "this is not expected to reflect the licenced posology".

Other aspects of the study methodology for TRAILBLAZER-ALZ and TRAILBLAZER-ALZ 2 are provided in CS Appendix CS Appendix I.1.1 Table 50 and CS Table 6 respectively. The two trials are similar in terms of methodology except for the features summarised in Table 7 below.

The TRAILBLAZER-ALZ RCT took place within the US and Canada and participants with high tau levels were excluded, whereas the TRAILBLAZER-ALZ 2 RCT took place in a wider range of countries and participants with high tau levels were not excluded. In response to clarification question A6 the company explained that people with no to very low tau were excluded from TRAILBLAZER-ALZ 2 and therefore this trial population is slightly enriched for a higher tau group than would be present in the general early symptomatic Alzheimer's disease population. Although the donanemab dosage was identical in the two studies, the timeframe over which the dose was administered was approximately 90 minutes in TRAILBLAZER-ALZ but in TRAILBLAZER-ALZ 2 only a minimum infusion time of 30 minutes was stated. The way permitted concomitant medications were handled also differed slightly between the studies as did the reporting of outcomes. For TRAILBLAZER-ALZ 2, outcomes were reported for the low-medium tau pathology population or the overall population or both. Our clinical experts agreed that the minor differences between trials would be unlikely to have an impact on trial outcomes.

Table 7 Summary of the differences between the methodology of the TRAILBLAZER-ALZ and TRAILBLAZER-ALZ 2 RCTs

	TRAILBLAZER-ALZ (Phase 2 RCT)	TRAILBLAZER-ALZ 2 (Phase 3 RCT)
Location	56 sites in the US and Canada	277 sites in 8 countries: US, Australia, Canada, Czech Republic, UK,[a] Japan, the Netherlands, and Poland
Key inclusion criteria	Meet flortaucipir/florbetapir F18 scan criteria. The flortaucipir scan inclusion criteria were: Standardized Uptake Value ratios of 1.10 to 1.46, inclusive, or <1.10 if	Meet flortaucipir/florbetapir F18 scan criteria. Baseline tau PET levels were defined using an SUVR value: **Intermediate tau**: SUVR ≤1.46 and [redacted]

	TRAILBLAZER-ALZ (Phase 2 RCT)	TRAILBLAZER-ALZ 2 (Phase 3 RCT)
	topographic deposition pattern consistent with advanced AD.	[redacted] or 1.10 ≤ SUVR ≤ 1.46 and [redacted] These values appear to be consistent with those for TRAILBLAZER-ALZ. High tau: SUVR >1.46 and [redacted] These participants would have been excluded from TRAILBLAZER-ALZ.
Method of study drug administration	Donanemab administered by IV infusion over a course of approximately 90 minutes.	Donanemab administered by IV infusion over a minimum of 30 minutes.
Permitted and disallowed concomitant medication	Use of approved or standard of care symptomatic treatments for AD was permitted during the study, provided that the dose had been unchanged for 2 months before Visit 2, and dosage should remain constant throughout the double-blind period.	Use of approved or standard of care symptomatic treatments for AD was permitted during the study, provided that the dose had been unchanged for at least approximately 30 days before randomisation. When medically indicated, initiation, increase or discontinuation of symptomatic treatments for AD was permitted.
Reporting of primary outcome	iADRS (change from baseline to 76 weeks).	iADRS (change from baseline to 76 weeks) in the low-medium tau pathology population or the overall population.
Reporting of key secondary efficacy endpoints	In the trial population.	In at least one of the low-medium tau pathology population or the overall population.
Enrolment and study completion.	Enrolment began December 2017 and the study completed September 2021.	Enrolment began 19th June 2020, and ended 5th November 2021, and database lock/unblinding (double blind phase) occurred on 28th April 2023.

Source: Combines data from CS Table 6 and CS Appendix I.1.1 Table 50
AD, Alzheimer's disease; CS, company submission; iADRS, integrated Alzheimer Disease Rating Scale; IV, intravenous; PET, positron emission tomography; SUVR, standardised uptake value ratio, UK, United Kingdom; US, United States.
[a] The CSR provides the numbers of participants from the UK: [redacted] in the placebo arm and [redacted] in the donanemab arm. Overall, [redacted] ([redacted]%) participants were from the UK.

3.2.1.2 Patients' baseline characteristics

Patient baseline characteristics for the TRAILBLAZER-ALZ trial and the TRAILBLAZER-ALZ 2 trial are presented in CS Appendix I.1.1 Table 54 and CS Table 7 respectively. The company does not comment on the data presented in these tables. We observe that within

each trial characteristics are well balanced between arms in the respective trials and our clinical experts agreed that the minor differences that can be observed would not be expected to impact on clinical outcomes.

Participant characteristics are expected to differ with respect to tau PET levels because people with high tau levels were excluded from the TRAILBLAZER-ALZ RCT whereas they were not excluded from the TRAILBLAZER-ALZ 2 RCT. As noted above TRAILBLAZER-ALZ 2 was slightly enriched for a higher tau population due to the exclusion of people with no to very low tau (company response to clarification question A6). In other respects, participant characteristics are very similar when the two trials are compared. Participants in the phase 3 TRAILBLAZER-ALZ 2 trial are on average a little younger (by about 2 years) and the trial enrolled a slightly higher proportion of women and more people who described themselves as Asian than in the phase 2 TRAILBLAZER-ALZ trial. In general, the mean baseline scores for clinical outcomes are slightly worse in the TRAILBLAZER-ALZ 2 trial. Our clinical experts did not believe that the slight differences between the participants in the two trials would impact on clinical outcomes.

We note that a high proportion (approximately 60%) of the participants in both trials were in receipt of an acetylcholinesterase inhibitor or memantine. The use of acetylcholinesterase inhibitors in people with MCI due to Alzheimer's disease and the use of memantine in people with either MCI or mild dementia due to Alzheimer's disease is outside the recommendations of NICE NG97.[10] In response to clarification question A7 the company indicated that in the TRAILBLAZER-ALZ 2 RCT 45.2% of participants with MCI were on acetylcholinesterase inhibitor therapy at baseline and 13.4% were taking memantine at baseline. As stated earlier, our clinical experts agreed that some people with MCI due to probable Alzheimer's disease would receive an acetylcholinesterase inhibitor off-label and the company's findings from the cross-sectional Adelphi survey ([redacted]% of MCI patients using off-label acetylcholinesterase inhibitors) seemed realistic. However, one clinical expert's experience was that less than 20% of people with MCI due to probable Alzheimer's disease would receive an acetylcholinesterase inhibitor off-label. Neither of our experts stated that patients with MCI received memantine in clinical practice. The use of acetylcholinesterase inhibitors and memantine in participants with MCI in the TRAILBLAZER-ALZ 2 RCT and the use of memantine for people with mild dementia due to Alzheimer's disease was therefore higher than estimated in UK clinical practice. In response to clarification question A1b the company confirmed that iADRS and CDR-SB change from baseline outcomes were not significantly

different for those who received acetylcholinesterase inhibitors or memantine at baseline and those who did not.

Table 8 Baseline demographics and clinical characteristics of participants in the TRAILBLAZER-ALZ and TRAILBLAZER-ALZ 2 trials

Characteristics[a]	TRAILBLAZER-ALZ (Phase 2 RCT, overall population)		TRAILBLAZER-ALZ 2 (Phase 3 RCT, overall population)	
	Donanemab (n=131)	Placebo (n=126)	Donanemab (n=860)	Placebo (n=876)
Sex, n (%)				
Women	68 (51.9)	65 (51.6)	493 (57.3)	503 (57.4)
Age, mean (SD), y	75.0 ± 5.6	75.4 ± 5.4	73.0 (6.2)	73.0 (6.2)
Race n (%)[b]				
American Indian or Alaska Native	0	0	2 (0.2)	0
Asian	1 (0.8)	2 (1.6)	57 (6.6)	47 (5.4)
Black[c]	5 (3.8)	3 (2.4)	19 (2.2)	21 (2.4)
White	122 (93.1)	121 (96.0)	781 (90.9)	807 (92.1)
Multiple	0	0	0	1 (0.1)
Missing	NA	NA	1 (0.1)	0
Other	3 (2.3)	0	NR	NR
Hispanic ethnic group, n or n/total N (%)[d]	5 (3.8)	3 (2.4)	35/618 (5.7)	36/630 (5.7)
Education of ≥13 y, n (%)	97 (74.0)	102 (81.0)	606 (70.5)	637 (72.8)
APOE ε4 carrier n/total N (%)	95/131 (72.5)	92/124 (74.2)	598/857 (69.8)[e]	621/872 (71.2)[e]
APOE genotype, n (%)[f]				
ε2/ε2	NR	NR	0	1 (0.1)
ε2/ε3	1/131 (0.8)	1/124 (0.8)	18 (2.1)	20 (2.3)
ε2/ε4	2/131 (1.5)	2/124 (1.6)	22 (2.6)	25 (2.9)
ε3/ε3	35/131 (26.7)	31/124 (25.0)	241 (28.1)	230 (26.4)
ε3/ε4	68/131 (51.9)	62/124 (50.0)	433 (50.5)	450 (51.6)
ε4/ε4	25/131 (19.1)	28/124 (22.6)	143 (16.7)	146 (16.7)
AChEI/memantine use, n (%)	78 (59.5)	74 (58.7)	521 (60.6)	538 (61.4)
Clinical outcomes,[g] mean±SD (range)				
iADRS score[h]	106.2±13.0 (60.0–130.0)	105.9±13.2 (67.0–139.0)	104.1±14.3	103.6±14.0
CDR-SB score	3.6±2.1 (0.5–11.0)	3.4±1.7 (0.5–8.0)	4.0±2.1	3.9±2.1
ADAS-Cog_{13} score	27.6±7.7 (10.0–51.0)	27.5±7.6 (5.0–47.0)	28.7±8.8	29.3±8.9
ADCS-ADL score[h]	67.4±8.6 (28.0–78.0)	67.0±8.1 (40.0–78.0)	66.3±8.6	66.4±8.3
ADCS-iADL score[h]	48.9±7.6 (21.0–59.0)	48.4±7.5 (24.0–59.0)	47.8±7.9	47.8±7.8
MMSE score[i,j]	23.6±3.1	23.7±2.9	22.4±3.8	22.2±3.9

Characteristics[a]	TRAILBLAZER-ALZ (Phase 2 RCT, overall population)		TRAILBLAZER-ALZ 2 (Phase 3 RCT, overall population)	
	Donanemab (n=131)	Placebo (n=126)	Donanemab (n=860)	Placebo (n=876)
	(14.0–29.0)	(16.0–29.0)		
Screening MMSE category, n (%)[k]				
MCI (≥27)	NR	NR	146 (17.0)	137 (15.7)
Mild AD (20–26)	NR	NR	713 (82.9)	738 (84.3)
Moderate AD (<20)	NR	NR	1 (0.1)	0
CDR-G score, n (%)				
0	NR	NR	2 (0.2)	4 (0.5)
0.5	NR	NR	514 (60.8)	532 (61.2)
1	NR	NR	304 (36.0)	308 (35.4)
2	NR	NR	25 (3.0)	25 (2.9)
Biomarker measures, mean±SD (range)				
Amyloid plaque level, Centiloids[l]	107.6±36.0 (41.0–251.4)	101.1±33.3 (38.7–225.2)	103.5±34.5	101.6±34.5
AD signature weighted neocortical flortaucipir SUVR[m]	NR	NR	1.34±0.25	1.35±0.26
Plasma P-tau217, pg/mL[n]	NR	NR	7.5±18.5	6.8±15.4
Global tau load on flortaucipir PET, mean (range)[p]	0.47±0.19 (0.1–1.2)	0.46±0.15 (0.2–0.9)	NR	NR

Source: The EAG has combined and edited two company tables: CS Appendix I.1.1 Table 54 and CS Table 7

AChEI, acetylcholinesterase inhibitor; AD, Alzheimer's disease; ADAS-Cog13, 13-Item Alzheimer's Disease Assessment Scale – Cognitive Subscale; ADCS-ADL, Alzheimer Disease Cooperative Study (Activities of Daily Living); ADCS-iADL, Alzheimer Disease Cooperative Study (Instrumental Activities of Daily Living); APOE, apolipoprotein E; CDR-G, Clinical Dementia Rating Global Score; CDR-SB, Clinical Dementia Rating Sum of Boxes; iADRS, Integrated Alzheimer Disease Rating Scale; MCI, mild cognitive impairment; MMSE, Mini-Mental State Examination; N, number; NA, not applicable; NR, not reported; PET, positron emission tomography; RCT, randomised controlled trial; SD, standard deviation; SUVR, standardised uptake value ratio; y, years

[a] Where percentages are reported these may not total 100 because of rounding.

[b] TRAILBLAZER-ALZ reported 'Race or ethnic group'. In both trials Race and ethic group were self-reported by the participants within fixed categories. The categories 'American Indian or Alaska Native' and 'multiple' were included for TRAILBLAZER-ALZ but do not appear in CS appendix I.1.1 Table 54 so we have presumed this is because zero participants selected either of these options. The TRAILBLAZER-ALZ 2 trial also reported Race for the US participants separately but this information, from CS Table 7, has not been reproduced here.

[c] CS Table 7 for the TRAILBLAZER-ALZ 2 trial reports 'Black or African American'

[d] In both trials Race and ethnic group were self-reported by the participants within fixed categories. For TRAILBLAZER-ALZ 2 the data in CS Table 7 are for Hispanic/Latino for the US participants only.

[e] total N calculated by EAG

[f] For the TRAILBLAZER-ALZ trial total N was 131 in the donanemab arm and 124 in the placebo arm. For TRAILBLAZER-ALZ 2 total N is not stated but the EAG has calculated this to be 857 in the donanemab arm and 872 in the placebo arm.

[g] See CS Table 5 and section 0 of this report for further details on each measure.

[h] For the iADRS, ADCS-ADL and ADCS-iADL measures in the TRAILBLAZER-ALZ trial data were available for 130 participants in the donanemab group.

[i] In the TRAILBLAZER-ALZ trial data were available for 126 participants in the donanemab group and 121 in the placebo group
[j] In the TRAILBLAZER-ALZ 2 trial this was the last non-missing MMSE score prior to or at the start of study treatment.
[k] Based on screening data. CS Table 7 also reports baseline MMSE category data (which is CIC information). In the baseline MMSE category data more patients have moderate AD (22.8% in the donanemab arm and 25.1% in the placebo arm).
[l] In the TRAILBLAZER-ALZ trial assessed with 18F-florbetapir PET, in the TRAILBLAZER-ALZ 2 trial assessed with 18F-florbetapir or 18F-florbetaben PET.
[m] Based on screening data and assessed with 18F-flortaucipir PET. Global tau uptake was measured using a composite neocortical SUVR with white matter signal reference.[33]
[n] Plasma P-tau217 denotes plasma-measured phosphorylated tau at threonine 217, a blood biomarker specific to Alzheimer disease and associated with both amyloid and tau pathology.[34]
[p] Data were available for 130 participants in the donanemab group, 124 in the placebo group

EAG comment on included studies

Of the three RCTs identified by the company's systematic literature review, two provide evidence for the clinical efficacy and safety of donanemab in comparison to placebo in participants who have MCI due to Alzheimer's disease or mild dementia due to Alzheimer's disease. The third trial's comparison, donanemab versus aducanumab, is not relevant to this appraisal but safety data for the participants who received donanemab are included in an integrated safety set. The CS focuses on presenting information and clinical effectiveness results from the phase 3 TRAILBLAZER-ALZ 2 trial with some summary information about the phase 2 TRAILBLAZER-ALZ trial presented in CS Table 4 and the remaining information in CS Appendix I. The company has only used clinical effectiveness evidence from the TRAILBLAZER-ALZ 2 trial to inform the economic model. We have compared the methodology of the two donanemab versus placebo trials and find these are broadly very similar. We also compared the characteristics of the participants enrolled in these trials and find that for the most part they are also very similar. The phase 3 RCT participants are likely a better representation of the people who will be treated with donanemab in clinical practice because participants with high tau pathology were not excluded from this trial but the company has stated that this trial was slightly enriched for a higher tau population that in the general early symptomatic Alzheimer's disease population. The phase 2 RCT excluded participants with high tau pathology so this trial's population represents a subset of the people who will be treated with donanemab in clinical practice. We note that the company does not expect that tau pathology will need to be assessed for donanemab to be administered in clinical practice. A high proportion of the participants in both trials were in receipt of an acetylcholinesterase inhibitor or memantine. In the

TRAILBLAZER-ALZ 2 RCT the use of acetylcholinesterase inhibitors and memantine in participants with MCI and the use of memantine for people with mild dementia due to Alzheimer's disease was higher than estimated in UK clinical practice. We raise this as a key issue (Key Issue 1). In both trials the result of PET scans during the double-blind treatment period could signal treatment step-down (TRAILBLAZER-ALZ only) or treatment completion. Whether this could occur in clinical practice will be dependent on PET scanning resources.

3.2.2 Outcomes assessment

We describe and critique the clinical efficacy, quality of life and safety outcomes assessed in the TRAILBLAZER-ALZ and TRAILBLAZER-ALZ 2 trials below, including the within-patient changes in cognition and function that the company considered to be a clinically meaningful.

3.2.2.1 Efficacy outcomes

We note that EMA guidance published in 2018 on the clinical investigation of medicines for treating Alzheimer's disease states that there is no ideal tool for assessing the efficacy of treatments for dementia, and that there is no reference technique for measuring cognitive and functional changes in Alzheimer's disease.[28] Therefore, the EMA considered that a range of measurement tools may be needed to assess treatment efficacy in a trial and that the choice of instrument should be adequately justified.[28] The EMA states that composite measures of cognition and function can be used in prodromal Alzheimer's disease/MCI due to Alzheimer's disease, but additional measures of cognition, function, executive function, instrumental activities and HRQoL should be considered among the secondary outcomes measures. However, the comprehensiveness of coverage of the measures used in a trial will depend on what is feasible. In established Alzheimer's disease, measures of cognition, activities of daily living (a functional outcome) and a global assessment of clinical response are recommended.[28]

The clinical efficacy outcomes measured in the TRAILBLAZER-ALZ and TRAILBLAZER-ALZ 2 trials are summarised in Table 9. Reflecting EMA guidance, a number of cognition and function measures were used, along with biomarker endpoints. In Table 9, the outcomes that were used in the company's economic model are highlighted in bold text.

Table 9 Summary of the clinical efficacy outcomes measured in the TRAILBLAZER-ALZ and TRAILBLAZER-ALZ 2 trials

Type of outcome	Specific outcome measures used [a]
Measures of cognition and function	iADRS change from baseline (primary outcome in both trials)
	CDR-SB change from baseline
	ADCS-iADL change from baseline
	ADAS-Cog$_{13}$ change from baseline
	MMSE change from baseline
Biomarker-related endpoints	**Change in amyloid plaque deposition from baseline as measured by florbetapir F18 PET scan[b]**
	Change in brain tau deposition from baseline as measured by flortaucipir F18 PET scan
	Change in volumetric MRI measures from baseline
Exploratory outcomes	Time-based analyses[c] of: • CDR-G • CDR-SB

Source: Partly reproduced from CS Tables 3, 4, 5 and 6, and Appendix I, Table 50
ADAS-Cog, 13-Item Alzheimer's Disease Assessment Scale – Cognitive Subscale; ADCS-iADL, Alzheimer's Disease Cooperative Study – Activities of Daily Living Inventory; CDR-G, Clinical Dementia Rating Global Score; CDR-SB, Clinical Dementia Rating Sum of Boxes; iADRS, Integrated Alzheimer's Disease Rating Scale; MMSE, Mini-Mental State Exam; MRI, magnetic resonance imaging; PET, positron emission tomography.
[a] Bold text shows the outcomes that inform the company's economic model base case. Only results from the TRAILBLAZER-ALZ 2 trial are used in the model (CS section B.3.2.2)
[b] The specific outcome used in the model is time to return to amyloid positivity levels, which informs the duration of full treatment effect after stopping treatment.
[c] Time-based analyses reported for the TRAILBLAZER-ALZ 2 trial only.

3.2.2.1.1 Measures of cognition and function

The CS provides a brief overview of the neuropsychological tests used in the TRAILBLAZER-ALZ 2 trial in CS sections B.2.3.1 and B.2.6.1 (i.e. these are the measures listed in Table 9 above), including total score ranges, how the scores are interpreted, and what is considered to be a meaningful within-person change on the measures in MCI due to Alzheimer's disease and mild dementia due to Alzheimer's disease (although no references are cited to support the selected thresholds). The company do not outline the score ranges on each measure that are used for defining normal cognition, MCI, mild dementia, moderate dementia and severe dementia due to Alzheimer's disease. We requested this information in clarification question A3 and the company provided the ranges where available (clarification response A3). In the absence of detailed information in the CS about the neuropsychological tests, we describe each of the measures below in more depth. We also provide the EAG's perspective on the company's selection of the CDR-SB measure to inform the treatment effectiveness estimates in the company's economic model.

Clinical expert advice to the EAG is that of the tests used in the TRAILBLAZER-ALZ trials, only the MMSE is used in clinical practice; none of the others are used outside of clinical trial

settings. We understand from one of our clinical experts that progression of Alzheimer's disease does not tend to be assessed in clinical practice, because while cognitive testing is informative pre-diagnosis, it is less useful afterwards as it is expected that people will experience a decline in their condition over time.

3.2.2.1.1.1 Integrated Alzheimer's Disease Rating Scale (iADRS)

The primary endpoint in both the TRAILBLAZER-ALZ and TRAILBLAZER-ALZ 2 trials was change from baseline on the iADRS at 76 weeks. The CS states that the iADRS measures both cognition and daily function, assessing the effect of cognitive loss on patients' abilities to engage in everyday activities (CS sections B.2 and B.2.6.1 and CS Table 5). A single summary score is calculated which provides a measure of global Alzheimer's disease severity (CS section B.2.6.1). Scores can range from 0 to 144, with a lower score indicating a greater level of disease severity (CS Table 5). This outcome is not used to inform the treatment effectiveness assumptions in the company's economic model.

Regarding the iADRS, the company state in CS section B.2.6.1 that *"The actual scales administered to participants in the trial were the ADAS Cog$_{13}$ and the ADCS ADL"*. The EAG notes that the iADRS measure was developed by combining the ADCS-iADL and the ADAS-Cog$_{13}$ scales and the total score on the iADRS is derived by summing the scores on these two measures[35] (please see sections 3.2.2.1.1.3 and 3.2.2.1.1.4 for a description of the ADCS-iADL and ADAS-Cog$_{13}$ scales, respectively). The iADRS was developed due to a stated need for measures that are more sensitive to assessing disease severity and progression in the early stages of dementia.[35] We note that many of the authors of a publication related to the development of the iADRS declared that they were employees or minor shareholders of Eli Lilly and Company in their published conflicts of interest.[35] The latter publication states that the measure is sensitive to changes in MCI due to Alzheimer's disease and mild dementia due to Alzheimer's disease, but its sensitivity to treatment effects in moderate dementia due to Alzheimer's disease has not been assessed. This is a potential limitation of the measure in trials of disease-modifying treatments where the aim is to assess disease progression over a longer-term period.

The iARDS is described more extensively in the clinical study report for TRAILBLAZER-ALZ 2 (CSR section 3.5.1).

3.2.2.1.1.2 Clinical Dementia Rating (CDR) scale

The Clinical Dementia Rating (CDR) scale is administered through a semi-structured interview with the patient and a patient supporter, such as a partner or adult child.[36; 37] It measures cognitive impairment in six areas: memory, orientation, judgement and problem solving, community affairs, homes and hobbies, and personal care. The level of impairment in these aspects is measured on a 5-point scale ranging from 0 (no impairment) to 3 (severe impairment).[37] There are two different ways of scoring the CDR: one provides the global CDR score (CDR-G) and the other the Sum of Boxes score (CDR-SB).[37] Both CDR-SB and CDR-G were used in the TRAILBLAZER-ALZ 2 trial. The CS states that the CDR-G is a clinical staging instrument and that the CDR-SB is an integrated measure of cognition and daily function (CS Table 5). We note the CDR-G is score is derived from following specific scoring rules that depend on whether the scores on the orientation, judgement and problem solving, community affairs, homes and hobbies, and personal care categories are the same as, less than or greater than the memory category score.[37] A score of 0 indicates no dementia, and scores of 0.5, 1, 2 and 3 indicate questionable dementia, mild, moderate and severe dementia, respectively.[37] The sum of boxes score is derived by summing the scores across the categories measured.[37] Scores can range from 0-18, with a higher score indicating a higher level of impairment (CS Table 5).

The CDR-SB can be used to measure the progression of dementia due to Alzheimer's disease[38] and it has been stated that an advantage of the CDR-SB over the global score is that offers increased accuracy when assessing changes over time.[39] Additionally, it has been found that the CDR-SB can be used to stage Alzheimer's disease.[39] Scores of 0.5 to 4.0 on the CDR-SB have been found to correspond to a score of 0.5 on the CDR-G, scores of 4.5 to 9.0 on the CDR-SB correspond to a score of 1.0 on the CDR-G, scores of 9.5 to 15.5 on the CDR-SB correspond to a score of 2.0 on the CDR-G, and scores of 16.0 to 18.0 on the CDR-SB correspond to a score of 3.0 on the CDR-G.[39] This largely aligns with the scoring ranges the company provided for this measure in clarification response A3, in which the company drew on one of the same references as us.

The CDR has been found to be a reliable and valid measure of disease severity stage when it is administered by a trained rater.[38; 40] The CDR-SB has been found to have acceptable test-retest reliability in MCI.[41]

Clinical expert advice to the EAG is that the CDR is not used in clinical practice; it is not used outside of clinical trial settings. It takes too long to be administered for it to be used routinely. We were advised that both the CDR-SB and CDR-G are a good representation of

how cognition and function are assessed in clinical practice and capture some of the same aspects as the tools that are used. One expert stated that the scales are based on the typical questions that a clinician would ask in practice.

Of the cognition and function measures used in the TRAILBLAZER-ALZ trials, the company opted to use the CDR-SB to inform the treatment effectiveness estimates in the company's economic model (specifically for the within-trial period; see section 4.2.9 for a detailed description of the time periods of the model and how the treatment effect was calculated and applied to each of these timepoints). The company argue that the CDR-SB is *"well-established"* and *"more widely recognised"* than the iADRS which was the primary outcome measure in the trials (CS section B.3.2.2). The hazard ratio for the risk of progressing to clinical worsening between the treatment arms at Week 76 from TRAILBLAZER-ALZ 2 was applied to transition probabilities in the model that were based on assumptions about the natural disease history of Alzheimer's disease (CS section B.3.2.2). The EAG and NICE asked the company in clarification question B5 for their rationale for selecting the CDR-SB measure to inform the treatment effectiveness assumption in the model instead of the other cognition and function measures used in the TRAILBLAZER-ALZ 2 trial. In clarification response B5, among their stated reasons, the company said that the use of this measure provided consistency in terms of mapping progression to the disease stages based on the CDR in the model and that it measures both function and cognition unlike the other measures in the trial. We provide our perspective on the selection of this measure in sections 3.2.2.1.1.6 and 4.2.9.

3.2.2.1.1.3 Alzheimer's Disease Cooperative Study-Instrumental Activities of Daily Living (ADCS-iADL)

The CS describes the ADCS-iADL as an assessment of function and states it is a subtest of the ADCS-ADL scale (CS Table 5). We note that the ADCS-ADL measures the ability of people living with Alzheimer's disease to carry out activities of daily living.[42] It can either be completed by a caregiver, or a clinician or researcher can carry out an interview with a caregiver to complete the measure. The iADL subscale measures the instrumental activities that a person living with dementia has carried out in the past four weeks and, if they have performed the activity, their rated level of competence in doing so.[42] The subscale has 16 items. CS Table 5 states that scores can range from 0 to 59, with a lower score indicating a greater degree of disease severity. We note that versions of the scale that are suitable for people with MCI and moderate-to-severe Alzheimer's disease have also been developed.[42]

3.2.2.1.1.4 13-item Alzheimer's Disease Assessment Scale – Cognitive subscale (ADAS-Cog$_{13}$)

CS Table 5 states that the ADAS-Cog$_{13}$ is a measure of cognition. We note that the ADAS-Cog is a subscale of the Alzheimer's Disease Assessment Scale (ADAS).[43] The ADAS-Cog is stated to be a widely used in Alzheimer's disease clinical trials.[43] The ADAS-Cog$_{13}$ is a modified version of the original ADAS-Cog.[43] The original measure included 11 tasks to be completed by the participant or rated by an observer.[43] Cognitive elements assessed include memory, language and praxis (praxis is the planning of movement to achieve a purpose).[43; 44] Individual tasks included in the ADAS-Cog are scored from 0 to 10, 0 to 4, 0 to 5, 0 to 8, 0 to 12 or 1 to 5, with scores determined by correct responses to the tasks or the observer's rating.[43] The ADAS-Cog$_{13}$ includes all 11 items included in the original measure, plus a task to assess delayed word recall and a number cancellation task or maze task.[43] Total scores can range from 0 to 85, with a higher score indicating greater disease severity (CS Table 5). The ADAS-Cog has been shown to have acceptable test-retest reliability in MCI.[41]

However, concerns have been raised that the ADAS-Cog is not sufficiently responsive for detecting treatment effects,[45] including in MCI where there may not be sufficient change in cognition that can be detected using the instrument compared to during the later stages of dementia where decline is more rapid, and in mild dementia.[44; 46] Therefore, it may underestimate the treatment effect.[47] It has been found that the ADAS-Cog$_{13}$ version is more responsive to treatment effects in people with MCI,[43] but other research suggests that there are concerns about how sensitive the measure is to changes in cognition in MCI and mild Alzheimer's disease.[48]

3.2.2.1.1.5 Mini-Mental State Exam (MMSE)

The CS states that the MMSE is a measure of cognitive function (CS Table 5). It includes 11 questions and takes around five to 10 minutes to administer.[49] There are two sections to the test: the first assesses orientation, memory and attention, and has a maximum score of 21, and the second assesses abilities to name, to follow both written and verbal instructions, to write a sentence and to copy a complicated figure.[49] The second part has a maximum score of nine. The CS states that scores on this measure can range from 0 to 30, with a lower score indicating greater disease severity.

The MMSE has been found to be valid and reliable,[49-51] but it has been found to have better criterion validity for detecting moderate-to-severe cognitive impairment than milder levels of impairment.[51] We note that an EAG report for TA217 ('Donepezil, galantamine, rivastigmine

and memantine for the treatment of Alzheimer's disease') states that the MMSE is insensitive to change in Alzheimer's disease, which may lead to an underestimation of a treatment effect.[47]

As stated above, our clinical experts said that the MMSE is the only neuropsychological test included in the TRAILBLAZER-ALZ 2 trial that is used in clinical practice. One expert noted, though, that it is not as widely used as it used to be.

3.2.2.1.1.6 EAG perspective on the use of the CDR-SB in the company's economic model

Given the considerations above, we are of the opinion that on balance that use of the CDR-SB measure to inform the treatment effect in the company's economic model is appropriate. The reasons for this are:

- Our clinical experts indicated that the CDR-SB adequately reflects how cognition and function are assessed in clinical practice and both thought it was an acceptable measure to inform treatment effectiveness in the economic model. One noted it has comparable results to the Alzheimer's Disease COMposite Score (ADCOMS)[52] (the latter scale was not used in the company's trials). Both experts felt that the CDR-SB is sensitive enough to detect disease progression in the early stages of Alzheimer's disease (i.e. in MCI due to Alzheimer's disease or mild dementia due to Alzheimer's disease).
- Both our clinical experts believe that the CDR-SB adequately captures factors that are important to patients living with MCI due to Alzheimer's disease and mild dementia due to Alzheimer's disease and their caregivers. One expert noted that the probably most important aspect of quality-of-life is not captured.
- It is a valid and reliable measure. One expert did raise a concern of a risk of under-estimation of group-level treatment effects, because patient-level effects may be larger.
- It can be used to measure disease progression.
- It has better accuracy for detecting change over time than the CDR-G.
- Concerns have been raised in the literature about the sensitivity of some of the other measures used in the TRAILBLAZER-ALZ trials (specifically, the MMSE and ADAS-Cog_{13}) to changes in Alzheimer's disease although one of our clinical experts thought more detailed scales, such as the ADAS-Cog, may be more sensitive and provide more nuance/detail than the CDR-SB.

- The iADRS appears to be a less well-established measure than the CDR-SB and we additionally note the concerns about the sensitivity of the ADAS-Cog_{13} noted in the bullet point and section 3.2.2.1.1.6 above which forms part of this scale.

However, while we believe use of the CDR-SB in the model is appropriate, obtaining additional clinical expert opinion during this appraisal about which measure most comprehensively captures disease progression in Alzheimer's disease would be informative. We have raised this as a key issue (Key Issue 2). We acknowledge that the CDR-SB was not the primary outcome measure of the trial, but we requested that the company include the iADRS measure as an outcome in the economic model and we present scenario analyses in section 6.3 using this measure.

3.2.2.1.1.7 Clinically meaningful benefit

The company detail what constitutes a meaningful within-patient change on each of the cognition and function measures used in the TRAILBLAZER-ALZ 2 trial for patients with MCI due to Alzheimer's disease and mild dementia due to Alzheimer's disease in CS Table 5. As stated above, the company do not provide references to support the selected thresholds. A minimal clinically important difference represents the within-person change that is considered to be clinically meaningful to patients.[53] That is, in the context of Alzheimer's disease, it defines what is thought to be a clinically meaningful decline.[54] In the TRAILBLAZER-ALZ 2 trial, the thresholds for the CDR-SB reported in CS Table 5 (and confirmed to be correct in the company response to clarification question B5b) were used to define clinical worsening in an analysis of the proportions of participants progressing on the CDR-SB (which was carried out using a Cox proportional hazards model analysis) [CS section B.2.6.5, clarification response B5a, Sims et al. (2023)[30] and TRAILBLAZER-ALZ 2 SAP]. The hazard ratio (HR) result from this analysis is used to inform the treatment effectiveness assumption in the company's economic model (CS sections B.2.6.5 and B.3.2.2).

The EAG have checked the meaningful within-patient change thresholds reported by the company for the CDR-SB against selected references in the literature. We note that minimal clinically important differences for the CDR-SB in MCI due to Alzheimer's disease and mild dementia due to Alzheimer's disease are reported in Andrews et al. (2019)[55] and Lansdall et al. (2023)[41] and we have reproduced the thresholds reported in these publications in Table 10, alongside the meaningful within-patient change values reported in CS Table 5, for

comparison. We have also included the reported minimal clinically important differences for the MMSE reported in these publications in the table, as this scale is used in clinical practice. Based on the minimal clinically important differences reported in Andrews et al. (2019)[55] and Lansdall et al.,[41] the thresholds selected by the company for the CDR-SB appear to be reasonable. Our clinical experts agreed that the thresholds for the CDR-SB appeared reasonable.

Table 10 Reported meaningful within-patient change and minimal clinically important differences for the CDR-SB and MMSE measures

Source	AD stage	Measure	
		CDR-SB	MMSE
MWPC reported in CS Table 5	MCI	1	-1
MCID reported in Andrews et al. (2019)[55]		0.98	-1.26 (95% CI -1.33 to -1.20)
Clinically meaningful change reported in Lansdall et al. (2023)[41]		1 [a] or 2.5 [b]	-2 to -3 [a] or -6 to -7 [b]
MWPC reported in CS Table 5	Mild AD	2	-2
MCID reported in Andrews et al. (2019)[55]		1.63	-2.32 (95% CI -2.41 to -2.24)
Clinically meaningful change reported in Lansdall et al. (2023)[41]		NR	NR

Source: Partly reproduced from CS Table 5, Andrews et al. (2019)[55] and Lansdall et al. (2023).[41]
AD, Alzheimer's disease; CDR-SB, Clinical Dementia Rating Sum of Boxes; CS, company submission; MMSE, Mini-Mental State Exam; MWPC, meaningful within-patient change; MCID, minimal clinically important difference; NR, not reported.
[a] Proposed 'minimal deterioration' threshold.
[b] Proposed 'moderate deterioration' threshold.

Regarding the MMSE scale, the value the company have selected for MCI appears to be relatively reasonable, based on that reported in Andrews et al. (2019)[55] and could be considered conservative in the context of the clinically meaningful change values reported by Lansdall et al. (2023).[41] However, one of our experts was of the opinion that the thresholds selected by the company for MCI and mild dementia were not fully reasonable for the MMSE. They believed a 1 to 2 point change on the MMSE was a minimal clinically important difference in MCI and that a 2 to 3 point change was a reasonable minimal clinically important difference in mild dementia due to Alzheimer's disease.

In terms of the primary outcome of the TRAILBLAZER-ALZ 2 trial, i.e. the iADRS, the company report in CS Table 5 that changes of -5 in MCI due to Alzheimer's disease and of -9 in mild dementia due to Alzheimer's disease is clinically meaningful. Although not cited in the CS, these values appear to come from a paper co-authored by Eli Lilly employees which reports the same MCIDs.[56] One of our experts commented that it is difficult to say what would be a clinically meaningful change on this measure.

A >20% slowing of disease progression has been regarded in the CS as a clinically meaningful change (CS sections B.2.3.1 and B.2.12.1). The company appear to apply the >20% threshold to interpret the clinical meaningfulness of the results of between-group analyses of the impact of donanemab on disease progression as measured by dividing the difference between donanemab and placebo least squares mean change values (baseline to week 76) by the least squares mean change from baseline with placebo at week 76 for the CDR-SB and iADRS (CS section B.2, 'Clinical Effectiveness Summary'). Clinical expert advice to the EAG is that the >20% slowing of disease progression definition is not used in clinical practice. Furthermore, we note that a publication presenting the European consensus on disease-modifying trials in Alzheimer's disease states that a reduction in the rate of disease progression of 30% to 50% would be a reasonable goal.[57]

When determining what is a clinically meaningful benefit of treatment, we were advised by one of our experts that patient-centred measures such as level of autonomy are a more relevant way of assessing this than using a >20% change in disease progression threshold. Similarly to our expert, we note that the Faculty of Public Health stated in their submission as part of this appraisal that a limitation of the clinically meaningful changes presented in the literature is that they are based on clinician's perspectives about what is important, rather than what is important to patients and their caregivers. However, the Faculty of Public Health stated that at the same time it is acknowledged that a quantifiable approach is needed.

Time-based analyses were also included in the CS, providing results for how long treatment with donanemab delayed disease progression. Our clinical experts agreed that time-saved or time-to-event analyses to describe a delay in progression are meaningful to patients and carers. Both experts thought that a delay in disease progression of about six months would be considered a meaningful benefit.

The discussion here and the perspectives provided in the professional organisation submissions for this appraisal present a range of considerations for how a clinically meaningful benefit may be conceptualised in this disease area. We raise this as an issue that may require further consideration (section 1.6).

3.2.2.1.2 Biomarker-related endpoints

As detailed in Table 9 above, the biomarker-related endpoints measured in the TRAILBLAZER-ALZ trials were change in amyloid plaque deposition from baseline as measured by the florbetapir F18 PET scan, change in brain tau deposition from baseline as measured by the flortaucipir F18 PET scan, and change in volumetric magnetic resonance imaging (MRI) measures from baseline. We focus on the change in amyloid plaque deposition outcome here, as it informs the economic model.

In the clinical effectiveness section of the CS, results from the TRAILBLAZER-ALZ 2 trial are presented for a) decrease in brain amyloid levels measured in Centloids (CL) on PET scan, and b) the proportion of participants with amyloid clearance (CS section B.2.6.3). In the trial, amyloid clearance was defined as <24.1 CL on amyloid PET scan (CS section B.2.6.3). CS section B.3.2.2 states that amyloid positivity is defined as >24.1 CL. The company justified this selected threshold in their response to clarification question B8 and provided a reference to support the use of the value (Navitsky et al. 2018).[58] One of our experts agreed with the definition used, but the other expert was not able to comment if it is in standard use and noted that different trials use different thresholds. This expert also noted that it may be important whether scans are read centrally or locally. The company acknowledged in their response to clarification B8 that other thresholds have been used in the literature (e.g. 24.6 CL), and stated that Lilly studies show that best thresholds lie between 24 and 25 CL. On the face of it the company's use of the 24.1 CL threshold appears reasonable, but there is some uncertainty about this and further clinical expert opinion may be needed. Clarity about how amyloid positivity is defined is important, because the >24.1 CL threshold is used in the company's economic model to estimate how long it takes to return to amyloid positivity (see section 4.2.9). Our clinical experts noted that PET and CSF testing have similar performance for detecting amyloid positivity for diagnostic purposes but one expert pointed out that only PET can be used to determine amyloid clearance.

We note that it has been found that reductions in amyloid levels do not necessarily improve cognition.[59]

3.2.2.2 HRQoL outcomes

The QoL-AD was used in the TRAILBLAZER 2 trial to measure patients' quality of life (CS Table 3). This measure is described in CS section B.2.6.5 as a disease-specific measure for assessing quality of life in people with Alzheimer's disease. The CS states it contains 13 items that assess different domains of a person's life, including their relationships, activities, mood, physical health and perceived capabilities to carry out tasks. These items are rated on

a scale from 1 to 4 (corresponding to ratings of poor to excellent). The measure can either be completed by the patient or by a proxy, such as a carer or family member. We note that it is a reliable and valid measure, and that it has been found that people with mild to moderate dementia can reliably and validly complete the assessment themselves.[60] QoL-AD data collected in TRAILBLAZER-ALZ 2 were not used in the company's economic model (CS Table 18); model utilities were sourced from the literature instead (please see section 4.2.10). Caregiver quality of life was not measured in the trial (CS Table 18).

3.2.2.3 Safety outcomes

Table 11 shows the safety assessments carried out in the TRAILBLAZER trials. The specific adverse events that were incorporated in the model were ARIA events, hypersensitivity, anaphylactic reaction and injection-related reactions (CS section B.3.2.4). The company also applied an additional risk of mortality due to treatment with donanemab to the first cycle of the model (CS section B.3.2.5).

ARIA-E and ARIA-H were adverse events of special interest. We define these ARIA events in section 2.2.1.4. In TRAILBLAZER-ALZ 2, MRIs were scheduled at weeks 4, 12, 24, 52 and 76 to monitor for ARIA. Unscheduled MRIs could also take place if the investigator judged these to be necessary. If ARIA was detected in a patient, they then underwent MRI every four to six weeks until the condition had resolved or stabilised (CS section B.2.3.2).

Table 11 Summary of safety assessments carried out in the TRAILBLAZER-ALZ and TRAILBLAZER-ALZ 2 trials

Safety assessment
Spontaneously reported AEs
MRI (ARIA and emergent radiological findings)
Clinical laboratory tests
Vital sign and body weight measurements
12-lead ECGs
Physical and neurological examinations
Infusion related reactions
C-SSRS

Source: Partly reproduced from CS Tables 3, 4 and 6, and Appendix I, Table 50.
AEs, adverse events; ARIA, amyloid-related imaging abnormality; C-SSRS, Columbia Suicide Severity Rating Scale; ECGs, electrocardiograms.
Bold text shows outcomes that inform the company's economic model base case. Only results from the TRAILBLAZER-ALZ 2 trial are used in the model (CS section B.3.2.4).

EAG comment on outcomes assessment

There appears to be no ideal reference measure of cognition and/or function in Alzheimer's disease. Given this and the other considerations above, we believe the company's use of the CDR-SB to inform the treatment effectiveness assumption in their economic model is acceptable. However, further clinical expert opinion about this may be beneficial and we raise this as a key issue (Key Issue 2).

Overall, what constitutes a clinically meaningful benefit of treatment in Alzheimer's disease does not appear to be well-defined and may require further discussion. The company's statement that a >20% change in disease progression is clinically meaningful is a lower benchmark than the goal set out by the European consensus on disease-modifying trials in Alzheimer's disease which suggests a slowing of disease progression of 30% to 50% would be reasonable. However, the company's selection of meaningful within-patient change thresholds for the analysis of the CDR-SB outcome that informs the economic model appears appropriate.

The company's use of the <24.1 Centloids (CL) scan threshold for defining amyloid clearance on amyloid PET also appears to be appropriate, but, again, further discussion about this with additional clinical experts may be beneficial.

3.2.3 Risk of bias assessment

The company provide a risk of bias assessment for TRAILBLAZER-ALZ 2 in CS section B.2.5 and for both the TRAILBLAZER-ALZ trials in CS Appendix B.3. The Cochrane risk-of-bias tool 2.0[61] was used, which is appropriate for assessing the risk of bias of RCTs. Table 52 in Appendix 2 shows the company's and the EAG's independent risk of bias assessments of the TRAILBLAZER-ALZ and TRAILBLAZER-ALZ 2 trials. When using the Cochrane risk of bias 2.0 tool, guidance is to specify the outcome that is being assessed for risk of bias.[61] The company has not stated in the CS which outcome they assessed. In our assessment of risk of bias here, we focus on the key secondary outcome of risk of participants progressing on the CDR-SB at Week 76 in the overall study population as this outcome (the HR from this analysis) informs the treatment effectiveness assumption used for the within-trial period in the company's economic model (see section 4.2.2). For the TRAILBLAZER-ALZ trial, we selected the LS mean change from baseline at Week 76 on the CDR-SB outcome reported in the trial CSR Table AACG.5.2 (that is, slowing of disease progression).

The EAG's assessment of the risk of bias associated with the two trials differs to the company's. The company gave both trials an overall rating of 'some concerns' but, as stated, we do not know which outcome the company have based their assessment on, while we judged both studies to be of an overall high risk of bias for the risk of participants progressing on the CDR-SB at Week 76. The company noted some concerns on the specific domain of bias related to deviations from the intended interventions (i.e. performance bias) due to the potential for study unblinding due to ARIA events in both trials (CS Appendix B.3). We agreed that this potential for unblinding exists, but we did not believe that this presented a risk of performance bias. Instead, our concerns related to the potential impact of unblinding due to ARIA events and infusion-related reactions on the assessment of the CDR outcome (i.e. detection bias). This may have been mitigated to some extent in the TRAILBLAZER-ALZ 2 trial, as CDR raters were blinded to adverse events information.[30] However, the measure is completed through an interview with patients and their supporters (see section 3.2.2) and it is unclear how these individuals would have been prevented from becoming aware of the treatment assignment when adverse events occurred. If patients and carers became aware of the treatment assignment, this could conceivably impact their responses to the CDR assessment. Concerns about the potential impact of unblinding due to side effects in trials of monoclonal antibodies in Alzheimer's disease on measures of cognition have been raised in the literature.[62]

We additionally rated both studies as having some concerns of a risk of bias due to missing outcome data (i.e. attrition bias). The proportion of participants who discontinued the trials due to adverse events differed between the donanemab and placebo arms, with a higher proportion of participants randomised to donanemab discontinuing for this reason. It is possible therefore that missingness in the outcome is related to its true value. For example, those who discontinued due to adverse events may have had different treatment outcomes than those who did not discontinue for this reason. However, for TRAILBLAZER-ALZ 2 the company did conduct sensitivity analyses for the ITT population under the missing at random assumption and the missing not at random assumption and provided the results of these analyses (presented in section 3.2.5) which both show donanemab slowed the progression of disease relative to the participants receiving placebo.

In relation to the TRAILBLAZER-ALZ trial, we additionally identified that the LS mean change from baseline at Week 76 on the CDR-SB outcome was not analysed in full accordance with the planned analysis approach [redacted]. This led us to consider that there were some concerns regarding bias in selection of the reported result.

In summary, the EAG are of the opinion that both the TRAILBLAZER-ALZ trials are at a high risk of bias for the key secondary outcome of risk of participants progressing on the CDR-SB at Week 76 which informs the economic model, due to high risk of detection bias. We also have some concerns about attrition bias in both trials and reporting bias in relation to the TRAILBLAZER-ALZ trial. We raise this as a key issue (Key Issue 4).

3.2.4 Statistical methods of the included studies

The statistical methods for the TRAILBLAZER-ALZ study are not presented in the CS but some information is available in the published paper for this RCT[63] and the company supplied the statistical analysis plans for both trials in response to clarification question A14. A summary of the statistical methods used in the trials and the EAG comments on these is provided below in Table 12.

Table 12 Summary and EAG critique of the statistical methods used in the TRAILBLAZER-ALZ and TRAILBLAZER-ALZ 2 RCTs

TRAILBLAZER-ALZ	TRAILBLAZER-ALZ 2
Analysis populations	
mITT population: participants who had a baseline and at least one post-baseline iADRS score. Safety population: participants who received at least one dose of randomized study treatment.	Evaluable efficacy (mITT) population[a]: All randomised participants with a baseline and at least one post-baseline efficacy measurement. Safety population: all randomised participants who are exposed to study drug.
EAG comment: In TRAILBLAZER-ALZ: The trial publication, Mintun et al.[27] states one placebo group participant (0.4% of the total 257 participants randomised to either placebo or donanemab) was not included in the modified intention-to treat population but for the iADRS outcome (Mintun et al.[27] Figure 2 Panel A) only 245/257 (95%) of the participants provide data at week 0. For TRAILBLAZER-ALZ2 CS Table 8 shows the size of the evaluable efficacy (mITT) population differed by outcome, presumably because some participants had at least one post-baseline measurement for the iADRS but not the CDR-SB or vice-versa, although this is not explicitly stated in the CS. For the iADRS the mITT population comprised [redacted]/1736 ([redacted]%) of the randomised participants and for the CDR-SB [redacted]/1736 ([redacted]%) of the randomised participants.	
Sample size calculations	
The trial publication, Mintun et al.[27] states that with 250 participants enrolled and the	The sample size calculation is described in CS Table 9. It was based on the low-

TRAILBLAZER-ALZ	TRAILBLAZER-ALZ 2
expectation that 200 would complete the trial there would be approximately 84% power to show a posterior probability of at least 0.6 that the donanemab arm will have at least 25% slower disease progression than the placebo arm (as measured by the iADRS score). The trial publication also reports the assumptions upon which the power calculation is based.	medium tau pathology population. With 1000 randomised participants in the low-medium tau pathology population the NCS2 model provides more than 95% power to show statistical significance for donanemab relative to placebo in iADRS at month 18. A 30% discontinuation rate was assumed.[30]
EAG comment: For TRAILBLAZER-ALZ the required number of participants were randomised but slightly fewer than expected completed the trial (Mintun et al.[27] Figure 1 shows 187 completed the trial, 13 fewer than expected). For TRAILBLAZER-ALZ2 1,182 low-medium tau pathology participants were randomised, exceeding the target sample size by 182 participants. Overall 1320 (76%)[30] participants completed the study but it is not clear how many of these were in the low-medium tau pathology subgroup (the EAG notes that overall 24% did not complete the study which is less than was assumed for the sample size calculation). Therefore, in both trials the target sample sizes for randomisation were reached. Although slightly fewer participants completed TRAILBLAZER-ALZ than expected the EAG expects that both trials were sufficiently powered for their primary outcomes.	
Methods to account for multiplicity	
The trial publication, Mintun et al.[27] indicates that the type 1 error rate for the primary outcome and key secondary outcomes was controlled using the graphical approach of Bretz and Maurer. A diagram of the hypothesis testing scheme is available in the statistical analysis plan.[64] The plan, if the primary analysis was statistically significant, was that the MMRM analyses would be conducted and statistical significance determined based on the order of the outcomes in the multiplicity graph of hypotheses: CDR-SB, ADAS-Cog_{13}, iADL and MMSE.	CS section 2.4.2 states that all secondary efficacy endpoints were controlled for multiplicity (gated) except for MMSE. The statistical analysis plan provided in response to clarification question A14 gives greater detail. The prespecified hypothesis testing plan used the graphical approach of Bretz et al.[65; 66] and a diagram of the hypothesis testing scheme is included. This scheme allowed for testing the outcomes in a prespecified order for both the overall trial population and the intermediate tau level population.

TRAILBLAZER-ALZ	TRAILBLAZER-ALZ 2
EAG comment: Appropriate procedures were used in both trials to minimise the risk of statistically significant effects being detected by chance.	
Analysis of outcomes	
The primary outcome and secondary outcomes were analysed with a mixed-effect model for repeated measures (MMRM). The model included terms for: baseline score, investigator, trial group, visit, interaction of trial group with visit, interaction of baseline score with visit, concomitant use of acetylcholinesterase inhibitors or memantine or both at baseline (yes or no), and age at baseline. To compare trial groups Fisher's exact test was used for postbaseline categorical data and an analysis of covariance model was used for postbaseline continuous data.	Randomisation was stratified by tau pathology (low-medium versus high) and the primary analysis was conducted in the mITT population for both the low-medium tau population and the overall tau population (i.e. low-medium and high tau groups combined) The primary outcome was analysed by both a natural cubic spline model with two degrees of freedom (NCS2) and a mixed-effect model for repeated measures (MMRM) and results from both analyses are reported. The MMRM was adjusted for: age, baseline value, visit as a categorical variable, treatment, baseline × visit interactions, treatment × visit interactions, concomitant acetylcholinesterase inhibitor/memantine use at baseline (CDR-SB only), and randomization stratifying factors of pooled site and, for combined population only, baseline tau category. For the vMRI outcome, only age and baseline brain volumes were covariates. Secondary outcomes were also analysed by NCS2 and MMRM for the overall population and the low-medium baseline tau subgroup. The CS states the MMRM analysis was the main analytical approach

TRAILBLAZER-ALZ	TRAILBLAZER-ALZ 2
	for the CDR-SB but NCS2 analysis was the main analytical approach for the remaining secondary outcomes. Biomarker secondary outcomes change from baseline to post-baseline visit was evaluated with an MMRM model.
EAG comment: The statistical models used for outcome analysis of the primary and secondary outcomes appear appropriate.	
Handling of missing data	
Individual items missing from scales used to measure cognition and function: [redacted] Other missing data: A likelihood-based MMRM was used to handle missing data. [redacted]	In answer to clarification question A15 the company stated that no imputation of missing values was performed for the primary analysis in the evaluable efficacy set. Sims et al.[30] states that a likelihood-based MMRM was used to handle missing data for the NCS and MMRM analyses. Individual items missing from scales used to measure cognition and function: Imputation rules were used to impute missing items. If there were more missing items than defined by the statistical analysis plan the total score for the scale was considered missing at that visit.
EAG comment: Although the company's approach to handling missing data appears broadly appropriate there is a lack of clarity on the methods used in TRAILBLAZER-ALZ 2. Our assumption is that missing values were not imputed for the primary analysis in the evaluable set but instead were handled within the analysis itself via the likelihood-based MMRM under the assumption that the data were missing at random. However, it is likely that some data are missing not at random and thus the treatment effect could be overestimated. Therefore, sensitivity analyses should be conducted under alternative assumptions about missing data (see next item below).	
Sensitivity & post-hoc analyses	

TRAILBLAZER-ALZ	TRAILBLAZER-ALZ 2
[redacted]	Two sensitivity analyses for the using different assumptions about missing data were conducted for the ITT population which are described in the company's answer to clarification question A16 and the results from these analyses are provided. The CSR indicates [redacted]
EAG comment: The use of sensitivity analyses in the TRAILBLAZER-ALZ 2 trial appear to be appropriate.	

Source: EAG created table
CDR-SB, Clinical Dementia Rating Sum of Boxes; CS, company submission; CSR, clinical study report; EAG, external assessment group; EMA, European Medicines Agency; iADRS, Integrated Alzheimer Disease Rating Scale; MMRM, mixed-effect model for repeated measures; MMSE, Mini-Mental State Examination; NCS, natural cubic spline model; NCS2, natural cubic spline model with two degrees of freedom
[a] The company define six analysis populations in CS Table 8. In response to clarification question A13 the company confirmed that the primary analysis was conducted in the evaluable efficacy population (which after CS Table 8 is referred to as the mITT population).

EAG comment on study statistical methods

From the information that is available, standard methods appear to have been used appropriately and the EAG has not identified any major concerns about the statistical methods used in the two trials.

3.2.5 Efficacy results of the intervention studies

3.2.5.1 iADRS change from baseline to 76 weeks (Primary outcome)

In both the TRAILBLAZER-ALZ and the TRAILBLAZER-ALZ 2 trials there was a smaller reduction in iADRS scores (indicating less cognitive and functional decline) from baseline to 76 weeks in the donanemab trial arm than in the placebo arm (Table 13). The least-square

mean difference in iADRS score (which ranges from 0 to 144) versus placebo was 3.20 points (95% CI 0.12 to 6.27; p = 0.04) in the TRAILBLAZER-ALZ trial and 2.92 points (95% CI 1.51 to 4.33, p<0.001) in the TRAILBLAZER-ALZ 2 trial. The change in iADRS scores over the 76 week trial period is presented in Mintun et al. 2021[27] (Figure 2, Panel A) for TRAILBLAZER-ALZ and CS Figure 6 for TRAILBLAZER-ALZ 2. These figures also show the number of trial participants contributing data at each timepoint. The slowing of clinical progression was calculated as 31.8% in the TRAILBLAZER-ALZ trial by the EAG using the same method the company reports for their calculation of slowing of clinical progression for the TRAILBLAZER-ALZ 2 trial of 22.3%. Within the CS a greater than 20% slowing of progression has been taken to be clinically meaningful. The company's benchmark for the slowing of clinical progression has therefore been met by both trials for the iADRS outcome. However, we are aware that there is debate amongst the clinical community, with some suggesting that greater than 30% slowing of progression would be clinically meaningful (see section 3.2.3.1.1.7 of this report for a discussion about this). Only the TRAILBLAZER-ALZ trial would meet this higher benchmark for the iADRS outcome.

Table 13 iADRS change from baseline to 76 weeks

	TRAILBLAZER-ALZ		**TRAILBLAZER-ALZ 2**	
	Donanemab	**Placebo**	**Donanemab**	**Placebo**
Least-squares mean change from baseline to 76 weeks (95% CI)	−6.86 (−9.08 to −4.64)[a]	−10.06 (−7.82 to −12.30)[a]	−10.19 (−11.22 to −9.16)	−13.11 (−14.10 to −12.13)
Least-squares mean difference versus placebo in iADRS score (95% CI, p-value)	3.20 (0.12 to 6.27; p = 0.04)		2.92 (1.51 to 4.33, p<0.001)	

Source: EAG created table, using data for TRAILBLAZER-ALZ sourced from CS Appendix section I.1.2.1 and for TRAILBLAZER-ALZ 2 sourced from CS Table 11.
CI, confidence interval; iADRS, Integrated Alzheimer's Disease Rating Scale
[a] Calculated by the EAG from the SE in Table S3 of the appendix to the Mintun et al. paper[27] (95% CI comprises the values 1.96xSE either side of the mean)

In response to clarification question A16 the company present the methods and results of ITT sensitivity analyses for TRAILBLAZER-ALZ 2 conducted under the missing at random assumption or the missing not at random assumption. As Table 14 shows, in the missing at random assumption analysis based on the ITT population, the results for the least-squares mean change difference [redacted] in the primary analysis for the mITT population [redacted] compared to 2.92, 95% CI 1.51 to 4.33, p<0.001). With the

missing not at random assumption the least-squares mean change difference [redacted] in the primary analysis for the mITT population [redacted]

Table 14 Analysis results for TRAILBLAZER-ALZ 2 iADRS (NCS2) at week 76 using two different imputation methods

Analysis (based on ITT population)	Donanemab versus placebo	
	LS mean change difference (SE, 95% CI)	p-value
Missing imputation with missing at random assumption [a]	[redacted]	[redacted]
Missing imputation with a missing not at random assumption [b]	[redacted]	[redacted]

Source: Adapted by the EAG from the company's response to clarification question A16, Table 8
CI, confidence interval; ITT, intention-to-treat; LS, least squares; SE, standard error
[a] LS mean change from baseline, SE, 95% CI and p-value are derived using natural cubic spline model with 2 degree of freedom. The model was adjusted for basis expansion terms (two terms), basis expansion term-by-treatment interaction, and covariates for age at baseline, pooled investigator, baseline tau category, and baseline AChI/Memantine use. Imputation method: multiple imputation with indicators of discontinued treatment and ARIA occurrence as covariates
[b] LS mean change from baseline, SE, 95% CI and p-value are derived using natural cubic spline model with 2 degree of freedom. The model was adjusted for basis expansion terms (two terms), basis expansion term-by-treatment interaction, and covariates for age at baseline, pooled investigator, baseline tau category, and baseline AChI/Memantine use. Imputation method: If patient discontinued due to death or ARIA, multiple imputation using observed values from the lower 20% of change scores seen in the whole trial; otherwise, impute with a jump to reference.

3.2.5.2 CDR-SB change from baseline to 76 weeks (Key secondary outcome)

As Table 15 shows, the change in CDR-SB from baseline to 76 weeks was smaller in the donanemab trial arm in comparison to the placebo arm of each trial as indicated by the negative LSM change difference values (higher scores on the CDR-SB indicate a higher level of impairment). The difference between the groups was not statistically significant in the TRAILBLAZER-ALZ trial[27] but there was a significant difference in the TRAILBLAZER-ALZ 2 trial. The change in CDR-SB scores over time and the number of participants contributing data to each timepoint is presented in Mintun et al. 2021[27] (Figure 2, Panel B) for TRAILBLAZER-ALZ and CS Figure 7 for TRAILBLAZER-ALZ 2. The slowing of clinical progression measured by the CDR-SB has been calculated by the EAG as 22.8% for TRAILBLAZER-ALZ and is reported as 28.9% (95% CI 18.41, 39.44) by the company (CS Table 11). Both trials are considered to show a clinically meaningful slowing of progression for the CDR-SB measure by the company whose benchmark is a greater than 20% slowing of progression. But if the benchmark were to be raised to greater than 30% slowing of

progression to be clinically meaningful, then neither trial would meet this. The company also cite evidence[67; 68] that a change versus placebo in the CDR-SB of -0.5 is an indication of clinical significance. Using this approach, the change difference at 76 weeks of -0.36 (95% CI −0.83 to 0.12) in the TRAILBLAZER-ALZ trial would not be considered clinically significant but the -0.70 (95% CI −0.95 to −0.45) in the TRAILBLAZER-ALZ 2 trial would be considered clinically significant.

Table 15 CDR-SB change from baseline to 76 weeks

	TRAILBLAZER-ALZ		**TRAILBLAZER-ALZ 2**	
	Donanemab	**Placebo**	**Donanemab**	**Placebo**
LS mean change (95% CI)	1.22 (0.88 to 1.56)[a]	1.58 (1.23 to 1.93)[a]	1.72 (1.53 to 1.91)	2.42 (2.24 to 2.60)
LSM change difference (95% CI; p-value)	−0.36 (−0.83 to 0.12; p=0.139)		−0.70 (−0.95 to −0.45; p<0.001)	

Source: EAG created table
CDR-SB, Clinical Dementia Rating Sum of Boxes; CI, confidence interval; LS, least squares; LSM, least squares mean
[a] Calculated by the EAG from the SE in the CSR (95% CI comprises the values 1.96xSE either side of the mean)

As described above for the iADRS, in response to clarification question A16 the company presented sensitivity analyses for TRAILBLAZER-ALZ 2 ITT population conducted under the missing at random assumption or the missing not at random assumption. The sensitivity analyses for the CDR-SB outcome have a similar pattern to those for the iADRS outcome. In the missing at random assumption analysis the results for the least-squares mean change difference [redacted] in the primary analysis for the mITT population [redacted] compared to −0.70, 95% CI −0.95 to −0.45. With the missing not at random assumption the least-squares mean change difference [redacted] in the primary analysis for the mITT population [redacted] (Table 16).

Table 16 Analysis results for TRAILBLAZER-ALZ 2 CDR-SB (MMRM) at week 76 using two different imputation methods

Analysis (based on ITT population)	Donanemab versus placebo	
	LS mean change difference (SE, 95% CI)	p-value
Missing imputation with missing at random assumption [a]	[redacted]	[redacted]
Missing imputation with a missing not at random assumption [b]	[redacted]	[redacted]

Source: Adapted by the EAG from the company's response to clarification question A16, Table 8
CI, confidence interval; ITT, intention-to-treat; LS, least squares; SE, standard error
[a] LS mean change from baseline, SE, 95% CI and p-value are derived using mixed model repeated measures methodology with fixed factors for treatment, visit, treatment-by-visit interaction, and covariates for baseline score, baseline score-by-visit interaction, baseline tau category, pooled investigators, concomitant AchEI or memantine use at baseline, and age at baseline. Imputation method: multiple imputation with indicators of discontinued treatment and ARIA occurrence as covariates
[b] LS mean change from baseline, SE, 95% CI and p-value are derived using mixed model repeated measures methodology with fixed factors for treatment, visit, treatment-by-visit interaction, and covariates for baseline score, baseline score-by-visit interaction, baseline tau category, pooled investigators, concomitant AchEI or memantine use at baseline, and age at baseline. Imputation method: If patient discontinued due to death or ARIA, multiple imputation using observed values from the lower 20% of change scores seen in the whole trial; otherwise, impute with a jump to reference.

3.2.5.3 Analysis of clinical effectiveness results for the economic analysis

The company used a hazard ratio of disease progression based on the CDR-SB outcome as a measure of treatment effect in the economic model. The company estimated this hazard ratio using a Cox proportional hazard model based on data from the TRAILBLAZER-ALZ 2 RCT only. The company corrected the definition for the clinical worsening criteria that was used for this model originally provided in CS section B.2.6.5 in response to clarification question B5b stating that clinical worsening is defined as a "*1-point or more increase in CDR-SB from baseline for participants with baseline clinical status of MCI due to AD, or a 2-point increase from baseline for participants with baseline clinical status of mild AD dementia*". The baseline clinical status of MCI due to AD or mild AD dementia was based on participants' screening MMSE value. We note that one participant in the donanemab arm of TRAILBLAZER-ALZ 2 had a screening MMSE category of 'moderate' so this participant may have been excluded from the analysis.

Participants had to meet the clinical worsening criteria at two consecutive visits during the double blinded phase to meet the criteria for a clinical worsening event. CS Figure 10 shows the proportion of participant progressing on the CDR-SB. The Cox proportional hazards

model was fitted to the TRAILBLAZER-ALZ 2 data to evaluate the hazard of progressing to the defined clinical worsening events for each trial arm. We asked the company to provide evidence that the proportional hazard assumption holds (clarification question B7). From the company's response to clarification question B7 (which can be seen in the accompanying papers for this appraisal) we agree that the assumption of proportion hazards is appropriate. The analysis was modelled as time to first occurrence of the clinical worsening event and adjusted for the covariates of: baseline age, score (the CS does not state which score, from details of the model provided in the published paper[30] this may be baseline CDR-SB score) and concomitant acetylcholinesterase inhibitors and /or memantine use at baseline (yes/no). The model was also stratified by pooled investigator sites and baseline tau category (randomisation for TRAILBLAZER-ALZ 2 was stratified by both of these factors).

The result from the Cox proportional hazards model analysis of progressing to clinical worsening using the CDR-SB measure was a hazard ratio of 0.62 (95% CI 0.52 to 0.75) (i.e. a 38% lower risk of progression based on the CDR-SB) and this hazard ratio is used in the economic model as described in section 4.2.9.1.

We asked the company to add an option to the economic model of applying a hazard ratio of disease progression based on the iADRS outcome (clarification question B5c). The hazard ratio analysis was modelled in the same way as described above (with the same covariates) for the CDR-SB but for the iADRS clinical worsening was defined as a "*≥5-point decrease in iADRS for MCI due to AD and a ≥9-point decrease in iADRS for mild AD dementia participants*". It was also necessary for the clinical worsening criteria to be met at two consecutive visits during the double-blind phase of the TRAILBLAZER-ALZ 2 trial for participants to meet the criteria for a clinical worsening event. In their response to clarification question B5c the company states that the proportional hazards assumption also holds for this model although they did not provide the evidence for this. The result from the Cox proportional hazards model analysis of progressing to clinical worsening using the iADRS measure was a hazard ratio of 0.700 (95% CI 0.582 to 0.842).

3.2.5.4 Other secondary outcomes and results from alternative statistical methods

The results for the other clinical outcomes (ADCS-iADL, ADAS Cog_{13} and MMSE) are shown together with those for iADRS and CDR-SB for the TRAILBLAZER-ALZ (Table 17) and the TRAILBLAZER-ALZ 2 (Table 18) trials. Where alternative statistical methods were used to analyse the data, these results are also shown in the tables. In the TRAILBLAZER-ALZ study as already noted above, there was an improvement in iADRS score (MMRM analysis,

p=0.04) but there was no significant difference between the trial arms for the CDR-SB. The CDR-SB was the first secondary outcome tested in the pre-defined testing strategy (section 3.2.3) and thus although p values were calculated for subsequent outcomes, these must be considered nominal. The percentage of reduction values range from [redacted]% (for [redacted]) to [redacted]% for [redacted], so [redacted] of these outcomes achieve the company's benchmark for a clinically meaningful slowing of progression but [redacted] if a 30% slowing of progression is taken to be clinically meaningful. In the TRAILBLAZER-ALZ 2 trial (Table 18) all p-values vs placebo indicate a statistically significant difference. Three of the five outcomes (iADRS and CDR-SB as already described above in sections 3.2.5.1 and 3.2.5.2 and ADCS-iADL) achieve the company's benchmark for a clinically meaningful slowing of progression but none meet the higher threshold of 30%.

We asked our clinical experts how confident they were in the clinical effectiveness of donanemab when looking at the results of the two trials for five measures of cognitive and functional impairment used (iADRS, CDR-SB, ADCS-iADL, ADAS Cog_{13} and MMSE). One expert's opinion was that the results suggest a clinically meaningful benefit, the other expert was somewhat confident (stating 'maybe 50:50').

Table 17 TRAILBLAZER-ALZ: Clinical outcomes from baseline to 76 weeks

Outcome[a]	Statistical method	Donanemab			Placebo			LSM difference vs placebo (95% CI)	p value vs placebo	% of reduction[b]
		Mean (SD)		LSM change (SE)	Mean (SD)		LSM change (SE)			
		Baseline	76 Weeks		Baseline	76 Weeks				
iADRS		n=	n=		n=	n=				
	NCS2[c]									
	MMRM			-6.86			-10.06	3.20 (0.12, 6.27)	0.04	
CDR-SB		n=	n=		n=	n=				
	NCS2							[d]		
	MMRM							-0.36 (-0.83, 0.12)	[e]	
ADCS-iADL		n=	n=		n=	n=				
	NCS2									
	MMRM							1.21 (-0.77, 3.20)	[e]	
ADAS-Cog$_{13}$		n=	n=		n=	n=				
	NCS2							[d]		
	MMRM							-1.86 (-3.63, -0.09)	[e]	
MMSE		n=	n=		n=	n=				
	NCS2									
	MMRM							0.64 (-0.40, 1.67)	[e]	

Source: Format of table based on CS Table 11 but populated with data for TRAILBLAZER -ALZ from CS Appendix I.1.2.1 and the CSR

ADAS-Cog13, 13-Item Alzheimer's Disease Assessment Scale – Cognitive Subscale; ADCS-iADL, Alzheimer's Disease Cooperative Study – Activities of Daily Living Inventory; CDR-SB, Clinical Dementia Rating Sum of Boxes; CI, Confidence interval; iADRS, Integrated Alzheimer's Disease Rating Scale; LSM, Least-squares mean; MMRM, Mixed-effect model for repeated measures; MMSE, Mini-Mental State Exam; NCS2, Natural cubic spline model with 2 degrees of freedom; SD, Standard deviation; SE, Standard error.

[a] Clinical outcomes were scored as follows: ADAS-Cog13 scores range from 0 to 85, with higher scores indicating greater overall cognition deficit; ADCS-iADL range from 0 to 59, with lower scores indicating greater impairment in daily function; CDR-SB range from 0 to 18, with higher scores indicating greater clinical impairment; iADRS range from 0 to 144, with lower scores indicating greater impairment; and MMSE range from 0 to 30, with lower scores indicating greater level of impairment.

[b]

[c] The NCS statistical model with 2 degrees of freedom [redacted]

[d] In the CSR table that provided these results [redacted]

[e] There was no significant difference between the trial arms for the CDR-SB score. As this was the first secondary outcome to be analysed in the testing strategy it means that no definite conclusions can be drawn about the between group difference for the next outcome tested, the change in ADAS-Cog13 score. The ADCS-iADL and MMSE score results did not show any statistically significant difference between the groups.

Table 18 TRAILBLAZER-ALZ 2: Clinical outcomes from baseline to 76 weeks

Outcome[a]	Statistical method	Donanemab			Placebo			LSM difference vs placebo (95% CI)	p value vs placebo	Slowing of clinical progression % (95% CI)[b]
		Mean (SD)		LSM change (95% CI)	Mean (SD)		LSM change (95% CI)			
		Baseline	76 Weeks		Baseline	76 Weeks				
iADRS		n=775	n=583		n=824	n=653				
	NCS2[c]	104.55 (13.90)	96.98 (20.87)	−10.19 (−11.22, −9.16)	103.82 (13.88)	93.82 (20.38)	−13.11 (−14.10, −12.13)	2.92 (1.51, 4.33)	<0.001	22.3 (11.38, 33.15)
	MMRM[d]	104.55 (13.90)	96.98 (20.87)	−10.19 (−11.27, −9.11)	103.82 (13.88)	93.82 (20.38)	−13.22 (−14.27, −12.18)	3.03 (1.60, 4.47)	<0.001	22.9 (11.96, 33.92)
CDR-SB		n=794	n=598		n=838	n=672				
	NCS2	3.92 (2.06)	5.25 (3.21)	1.66 (1.48, 1.83)	3.89 (2.03)	5.80 (3.22)	2.33 (2.16, 2.50)	−0.67 (−0.92, −0.43)	<0.001	28.9 (18.26, 39.53)
	MMRM[c,d]	3.92 (2.06)	5.25 (3.21)	1.72 (1.53, 1.91)	3.89 (2.03)	5.80 (3.22)	2.42 (2.24, 2.60)	−0.70 (−0.95, −0.45)	<0.001	28.9 (18.41, 39.44)
ADCS-iADL		n=780	n=591		n=826	n=661				
	NCS2[c]	47.96 (7.85)	44.53 (11.06)	−4.42 (−5.05, −3.80)	47.98 (7.70)	43.30 (10.61)	−6.13 (−6.72, −5.53)	1.70 (0.84, 2.57)	<0.001	27.8 (13.48, 42.13)
	MMRM[d]	47.96 (7.85)	44.53 (11.06)	−4.57 (−5.24, −3.90)	47.98 (7.70)	43.30 (10.61)	−6.32 (−6.97, −5.67)	1.75 (0.86, 2.64)	<0.001	27.7 (13.37, 42.00)
ADAS-Cog$_{13}$		n=797	n=607		n=841	n=677				
	NCS2[c]	28.53 (8.78)	32.72 (12.44)	5.46 (4.91, 6.01)	29.16 (8.85)	34.53 (12.00)	6.79 (6.26, 7.32)	−1.33 (−2.09, −0.57)	<0.001	19.5 (8.23, 30.83)
	MMRM[d]	28.53 (8.78)	32.72 (12.44)	5.70 (5.10, 6.30)	29.16 (8.85)	34.53 (12.00)	7.05 (6.47, 7.63)	−1.35 (−2.14, −0.57)	<0.001	19.2 (7.99, 30.38)
MMSE		n=796	n=600		n=841	n=679				
	NCS2	22.52 (3.84)	20.71 (5.52)	−2.47 (−2.73, −2.20)	22.20 (3.90)	19.79 (5.51)	−2.94 (−3.20, −2.69)	0.47 (0.10, 0.84)	0.01	16.1 (3.49, 28.67)
	MMRM[d]	22.52 (3.84)	20.71 (5.52)	−2.75 (−3.05, −2.44)	22.20 (3.90)	19.79 (5.51)	−3.22 (−3.51, −2.93)	0.48 (0.08, 0.87)	0.02	14.8 (2.46, 27.06)

Source: Reproduction of CS Table 11 which in turn gives the source as Sims et al. (2023).[30]
ADAS-Cog13, 13-Item Alzheimer's Disease Assessment Scale – Cognitive Subscale; ADCS-iADL, Alzheimer's Disease Cooperative Study – Activities of Daily Living Inventory; CDR-SB, Clinical Dementia Rating Sum of Boxes; CI, Confidence interval; iADRS, Integrated Alzheimer's Disease Rating Scale; LSM, Least-squares mean; MMRM, Mixed-effect model for repeated measures; MMSE, Mini-Mental State Exam; NCS2, Natural cubic spline model with 2 degrees of freedom; SD, Standard deviation; SE, Standard error.
[a] Clinical outcomes were scored as follows: ADAS-Cog13 scores range from 0 to 85, with higher scores indicating greater overall cognition deficit; ADCS-iADL range from 0 to 59, with lower scores indicating greater impairment in daily function; CDR-SB range from 0 to 18, with higher scores indicating

greater clinical impairment; iADRS range from 0 to 144, with lower scores indicating greater impairment; and MMSE range from 0 to 30, with lower scores indicating greater level of impairment.
[b] The percentage of slowing of clinical progression was calculated by dividing the LSM change from baseline treatment differences at 76 weeks by the LSM change from baseline with placebo at 76 weeks and multiplying by 100. The CI was estimated using the Delta method.
[c] Gated outcome, also indicated via grey shaded cells.
[d] For MMRM analyses, 95%CIs for LSM changes were calculated with the normal approximation method.

3.2.5.5 Time-based analyses

The company present the delay in disease progression during the TRAILBLAZER-ALZ 2 RCT for the iADRS and CDR-SB outcomes in terms of months saved versus placebo over the 76-week trial period (CS Table 12). Using the iADRS measure donanemab delayed disease progression by 1.38 months (95% CI 0.46 to 2.3) and using the CDR-SB measure disease progression was delayed by 5.44 months (95% CI 3.90 to 6.98). The company states that time saved would be expected to increase over a longer time period but the EAG notes that the duration of the treatment effect and when and how this wanes over time is uncertain due to a lack of long-term evidence. This impacts the economic model and is discussed in section 4.2.9.2. Our clinical experts thought that a delay in disease progression of about six months would be considered a meaningful benefit but neither specified the time frame that this delay should occur in (i.e. is the delay of six months meaningful over the 76-week trial period or a longer time period?).

3.2.5.6 Biomarker endpoints

Changes in amyloid PET, tau biomarkers and volumetric magnetic resonance imaging (vMRI) are presented in CS section B.2.6.3. Of these biomarkers, only amyloid is used to inform the economic model so this is the only marker discussed here.

In the TRAILBLAZER-ALZ and TRAILBLZER-ALZ 2 trials donanemab decreased overall brain amyloid plaque level in comparison to placebo from baseline to 76 weeks (Table 19 and for TRAILBLAZER-ALZ 2 CS Figure 8). In both trials the proportion of participants with amyloid clearance at 76 weeks was much higher in the donanemab trial arms than in the placebo trial arms (Table 19 and for TRAILBLAZER-ALZ 2 CS Figure 9). These results were to be expected because donanemab targets a form of beta-amyloid that is only present in amyloid plaques. These data are not used directly in the economic model but CS section B.3.2.2 presents a subgroup analysis for participants from the TRAILBLAZER-ALZ 2 trial who achieved early amyloid clearance (<24.1 CL) at 24 or 52 weeks which supports the companies assumption that treatment effect is maintained after stopping treatment and we discuss this further in section 4.2.9.2.

Table 19 Changes in amyloid

	TRAILBLAZER-ALZ		TRAILBLAZER-ALZ 2	
	Donanemab	**Placebo**	**Donanemab**	**Placebo**
Reduction in amyloid plaque level from baseline to 76 weeks, centiloids (95% CI)	-84.13 (not reported)	0.93 (not reported)	-87.0 (−88.90 to −85.17)	-0.67 (−2.45 to 1.11)
Difference in adjusted mean change at week 76, centiloids (95% CI)	-85.06 (-92.68 to -77.43)		Not reported	
Proportion with amyloid clearance at 76 weeks, % (95% CI)	67.8% (not reported)	[redacted]% (not reported)	76.4% (72.87 to 79.57)	0.3% (0.08 to 1.05)

Source: CS section B.2.6.3, Mintun et al 2021[27] and the TRAILBLAZER-ALZ CSR,[29]
CI, confidence interval

3.2.5.7 HRQoL outcomes

Health-related quality of life (HRQoL) was measured using the Quality of Life in Alzheimer's Disease (QoL-AD) questionnaire in a subset of patients and their caregivers in TRAILBLAZER-ALZ 2. HRQoL was not measured in the phase 2 TRAILBLAZER-ALZ trial. Table 20 shows the differences between the LSM change in QoL-AD score at 76 weeks was not statistically significant for either patient-assessed or proxy-assessed QoL-AD. These data were not used in the economic model.

Table 20 Patient- and proxy-assessed QoL-AD in TRAILBLAZER-ALZ 2

	TRAILBLAZER-ALZ 2	
	Donanemab (n=860)	**Placebo (n=876)**
Number of patients contributing data	[redacted]	[redacted]
Patient-assessed: LSM change from baseline at 76 weeks	[redacted]	[redacted]
Difference in LSM change in patient-measured QoL-AD score at 76 weeks (95% CI)	[redacted] p[redacted]	
Number of caregivers contributing data	[redacted]	[redacted]
Proxy-assessed: LSM change from baseline at 76 weeks	[redacted]	[redacted]

	TRAILBLAZER-ALZ 2	
	Donanemab (n=860)	Placebo (n=876)
Difference in LSM change in proxy-measured QoL-AD score at 76 weeks (95% CI)	[redacted]	

Source: EAG created table from information in CS section B.2.6.4
CI, confidence interval; LSM, least squares mean, QoL-AD; Quality of Life in Alzheimer's Disease

3.2.5.8 Subgroup analyses

The NICE scope specified the following subgroups of to be of interest in this appraisal:

- APOE ε4 gene carrier status
- People with MCI due to Alzheimer's disease
- People with mild dementia due to Alzheimer's disease

Subgroup analyses by all these factors of the adjusted mean differences between the trial arms on the iADRS and CDR-SB at 76 weeks and of the percentage slowing of disease progression are presented in the CS for the overall TRAILBLAZER-ALZ 2 trial population (CS section B.2.7).

The CS additionally presents subgroup analysis results for the TRAILBLAZER-ALZ 2 low-medium tau population in CS Appendix C.1.1, as this is the same the population that was of focus in the TRAILBLAZER-ALZ trial.

As the CS cautions (CS section B.2.6.6), participant numbers included in some of the subgroup analyses are small, and thus the results may be subject to some uncertainty.

3.2.5.8.1 APOE ε4 gene carrier status

CS Figures 11 and 12 show the adjusted mean difference results between participants assigned to donanemab and those assigned to placebo on the iADRS and CDR-SB by APOE ε4 genotype carrier status in the overall TRAILBLAZER-ALZ 2 population. We have reproduced these results in Table 21 below. As shown in the table below and in the CS figures (where the confidence intervals associated with the adjusted mean differences are shown), APOE ε4 noncarriers and heterozygous carriers assigned to donanemab had improved iADRS and CDR-SB scores at 76 weeks compared to those in the same subgroups assigned to placebo with the confidence intervals not crossing zero (the line of indifference), whereas for homozygous carriers the confidence interval did cross the line of indifference for both outcomes.

Table 21 also shows that non-carriers and heterozygous carriers experienced a slowing of disease progression of 28.7% and 33.6% at 76 weeks, respectively, on the CDR-SB, while homozygous carriers had a 17.7% slowing of disease progression on this measure at this timepoint. This general pattern of results was also found for the percentage slowing of disease progression as measured by the iADRS (see Table 21). We raise the impact of APOE ε4 allele status as a key issue (Key Issue 5).

Table 21 Adjusted mean difference from placebo and percentage slowing of disease progression results at 76 weeks on the iADRS and CDR-SB in the TRAILBLAZER-ALZ 2 trial by APOE ε4 genotype

APOE ε4 genotype	iADRS		CDR-SB	
	Adj. mean diff. [a]	% slowing (95% CIs)	Adj. mean diff. [b]	% slowing (95% CIs)
Noncarrier	4.58	28.1 (12.18, 43.93)	-0.76	28.7 (11.25, 46.14)
Heterozygote	2.87	23.8 (7.92, 39.67)	-0.73	33.6 (18.13, 49.09)
Homozygote	1.01	9.3 (-21.89, 40.44)	-0.41	17.7 (-8.13, 43.62)

Source: Partly reproduced from CS Figures 11 and 12.
Adj., adjusted; CDR-SB, Clinical Dementia Rating Sum of Boxes; CIs, confidence intervals; diff., difference; iADRS, Integrated Alzheimer's Disease Rating Scale.
[a] See CS Figure 11 for the forest plot showing the confidence intervals for these values.
[b] See CS Figure 12 for the forest plot showing the confidence intervals for these values.

3.2.5.8.2 People with MCI due to Alzheimer's disease and mild dementia due to Alzheimer's disease

Table 22 presents the results for the subgroup analyses of the adjusted mean difference from placebo and percentage slowing of disease progression at 76 weeks by clinical stage, specifically, MCI due to Alzheimer's disease and mild dementia due to Alzheimer's disease. The results in Table 22, along with the confidence intervals presented for the adjusted mean difference results shown in CS Figure 11 and 12, show that the confidence intervals for the favourable treatment effect of donanemab in people with MCI due to Alzheimer's disease at 76 weeks cross the line of indifference for both the iADRS and CDR-SB. By contrast, the confidence intervals for the treatment effect in favour of donanemab for people with mild dementia due to Alzheimer's disease do not cross the line of indifference. On the CDR-SB measure for people with mild dementia due to Alzheimer's disease treated with donanemab the adjusted mean difference versus placebo was -0.68 at week 76 (which represents an improvement in the score), with participants experiencing a 32.5% (95% CIs 18.19% to 46.80%) slowing of disease progression. On the iADRS, these participants had a 19.2% (95% CIs 4.29% to 34.08%) slowing of disease progression.

Table 22 Adjusted mean difference from placebo and percentage slowing of disease progression results at 76 weeks on the iADRS and CDR-SB in the TRAILBLAZER-ALZ 2 trial by disease clinical stage (MCI due to Alzheimer's disease and mild dementia due to Alzheimer's disease)

Clinical stage	iADRS		CDR-SB	
	Adj. mean diff. [a]	% slowing (95% CIs)	Adj. mean diff. [b]	% slowing (95% CIs)
MCI	2.14	39.3 (-25.00, 103.58)	-0.29	30.4 (-31.57, 92.30)
Mild AD	2.25	19.2 (4.29, 34.08)	-0.68	32.5 (18.19, 46.80)

Source: Partly reproduced from CS Figures 11 and 12.
AD, Alheimer's disease; Adj., adjusted; CDR-SB, Clinical Dementia Rating Sum of Boxes; CIs, confidence intervals; diff., difference; iADRS, Integrated Alzheimer's Disease Rating Scale; MCI, mild cognitive impairment.
[a] See CS Figure 11 for the forest plot showing the confidence intervals for these values.
[b] See CS Figure 12 for the forest plot showing the confidence intervals for these values.

3.2.5.8.3 Results of other subgroup analyses of the overall TRAILBLAZER-ALZ 2 population

Among the other subgroup analysis results conducted in the overall TRAILBLAZER-ALZ 2 trial population reported in CS Figures 11 and 12, we note:

- At 76 weeks when cognition and function were measured by either the iADRS or CDR-SB among people aged <65, the confidence intervals were relatively wide, suggesting some uncertainty in the results but we note that the numbers of participants included in these analyses was small (donanemab, n = 63 or 64; placebo, n = 71).
- The confidence intervals cross the line of indifference for the treatment effect at week 76 in people with a BMI of ≥30 on either measure.
- The confidence interval for the treatment effect at 76 weeks in people with low/medium tau favouring donanemab did not cross the line of indifference, when measured by the iADRS while in those with high tau it did. However, when the CDR-SB was used to measure cognition and function, the confidence intervals for the treatment effects in favour of donanemab at 76 weeks did not cross the line of indifference for either of the subgroups.
- On the iADRS, there is a difference in the point estimates of the no medication use at baseline and medication use at baseline subgroups but confidence intervals of the two subgroups are overlapping. On the CDR-SB measure the results for the two subgroups are very similar. In clarification question A1(b), the company confirmed

that iADRS and CDR-SB change from baseline outcomes were not significantly different for those who received acetylcholinesterase inhibitors or memantine at baseline and those who did not.

-

3.2.5.8.4 Low-medium tau population

Tau pathology was a randomisation factor in the TRAILBLAZER-ALZ 2 trial and the low-medium tau population was specified to be a primary analysis population in addition to the overall trial population (CS Appendix C.1.1). The company therefore present results from this subgroup in CS Appendix C.1.1.

Subgroup analyses by tau status were not specified to be of interest in the NICE scope for this appraisal. Additionally, the company state that they do not expect that tau pathology will need to be assessed for donanemab to be administered in clinical practice (CS Appendix C.1.1). Our clinical experts stated that on the whole they do not expect that tau will be tested in clinical practice, with one expert indicating that assessing tau by PET in the NHS would likely be impossible. We therefore expect that the trial results from the overall trial population are of more relevance to this appraisal than the results from the subgroup analyses by low-medium tau status.

The subgroup analyses of the low-medium tau population in the TRAILBLAZER-ALZ 2, presented in CS Appendix C.1.1, show:

- A slowing of disease progression as measured by the iADRS and the CDR-SB at week 76, favouring donanemab [iADRS: 31.5% slowing of disease progression (95% CI, 19.90% to 50.23%); CDR-SB: 36.0% slowing of disease progression (95% CI, 20.76% to 51.15%)].
- Brain amyloid plaque levels decreased by 88.0 CL (95% CI, −90.20 to −85.87) in the donanemab arm compared with an increase of 0.2 CL (95% CI, −1.91 to 2.26) in the placebo arm at 76 weeks.
- At 76 weeks, 80.1% (95% CI, 76.12%-83.62%) of participants assigned to donanemab had amyloid clearance compared with 0% (95% CI, 0.00%-0.81%) of participants assigned to placebo.
- Disease progression was delayed by 4.36 months (95% CI, 1.87 to 6.85) with donanemab treatment when cognition and function was measured by the iADRS and 7.53 months (95% CI, 5.69 to 9.36) when the CDR-SB was used.

- When using the CDR-G, the HR for the risk of disease progression with donanemab treatment compared to placebo was 0.61 (95% CI, 0.47 to 0.80; p < 0.001) at 76 weeks, representing a 38.6% lower risk. The HR for the risk of disease progression when cognition and function are assessed using the CDR-SB is not presented in the CS.
- When measured by the CDR-SB, 47% of participants assigned to donanemab compared with 29% of those assigned to placebo showed no decline in their cognition and function at one year (p < 0.001).
-

Subgroup analysis results by different participant baseline characteristics (including APOE ε4 gene carrier status and clinical stage) in the low-medium tau population are also presented in the CS (CS Appendix C.1.2). Results of analyses of the adjusted mean difference at 76 weeks between the trial arms and percentage slowing of the disease, as measured by the iADRS are provided, but no corresponding analyses for the CDR-SB are presented (CS Appendix C.1.2). The results of these analyses (as provided in CS Appendix Figure 6) for the low-medium tau population show broadly the same pattern as was observed for the overall trial population.

3.2.5.9 Safety outcomes

Adverse event data are presented in the CS from:

- The TRAILBLAZER-ALZ trial (CS Appendix I.1.2).
- The TRAILBLAZER-ALZ 2 trial (CS section B.2.9).
- An integrated safety dataset of results from the TRAILBLAZER-ALZ, TRAILBLAZER-ALZ 2, TRAILBLAZER-ALZ LTE and the donanemab cohort from the TRAILBLAZER-ALZ 4 trial (CS section B.2.9).

The integrated safety set included all participants who had received at least one dose of the study drug, with the measurement period being from the first dose of donanemab to the end of the treatment time period, plus 57 days (CS section B.2.9). We note that although the CS states that the integrated safety dataset included all participants on donanemab or placebo who received at least one dose of study drug, the data presented in the CS for the integrated safety dataset are specifically for participants who received donanemab.

Table 23 summarises the adverse events that occurred in the donanemab trials, including those reported in the integrated safety dataset and in each of the TRAILBLAZER-ALZ and TRAILBLAZER-ALZ 2 trials individually. Rates of participants experiencing at least one

treatment-emergent adverse event or adverse events that occurred during the study period were relatively similar between the TRAILBLAZER-ALZ and TRAILBLAZER-ALZ 2 trial arms (ranging from 82.2% to 90.8%; see Table 23). However, rates of treatment and study discontinuations due to adverse events were proportionally higher in the donanemab arms than the placebo arms in these two trials. The integrated safety analysis found that overall [redacted] of participants assigned to donanemab discontinued treatment due to adverse events.

Rates of serious adverse events were similar between the donanemab and placebo arms, ranging from 15.8% to 17.6% across these arms in the TRAILBLAZER-ALZ and TRAILBLAZER-ALZ 2 trials (Table 23). Three deaths occurred in the TRAILBLAZER-ALZ trial: one in the donanemab arm and two in the placebo arm. [redacted]. In the TRAILBLAZER-ALZ 2 trial, 16 deaths occurred in the donanemab group compared with 10 in the placebo group. Three of the deaths in the donanemab arm and one in the placebo arm were considered to be related to the study treatment. The CS states that of the deaths considered to be related to study treatment, those in the donanemab group happened after ARIA and the death in the placebo group was due to arteriosclerosis. [redacted].[31] Overall, in the integrated safety analysis, [redacted] deaths were considered to be related to donanemab treatment, representing a death rate of [redacted].

Table 23 Summary of adverse events by treatment group that occurred in the TRAILBLAZER-ALZ and TRAILBLAZER-ALZ 2 trials and that are reported in an integrated safety dataset

Event, No. (%)	Donanemab All, Integrated Dataset (n=2,727)	Donanemab TB (n=131)	Placebo TB (n=125)	Donanemab TB2 (n=853) [a]	Placebo TB2 (n=874) [a]
Deaths [b]	[redacted]	1 (0.8)	2 (1.6)	16 (1.9) [c]	10 (1.1)
Death considered related to treatment	[redacted] [f]	[redacted] [e]	[redacted] [e]	3 (0.4) [f]	1 (0.1) [f]
Participants with ≥1 serious AE [g]	[redacted]	23 (17.6)	22 (17.6)	148 (17.4)	138 (15.8)
Treatment discontinuations due to AEs	[redacted]	40 (30.5)	9 (7.2)	112 (13.1)	38 (4.3)
Study discontinuations due to AEs	[redacted]	20 (15.3)	6 (4.8)	69 (8.1)	32 (3.7)
Participants with ≥1 treatment-emergent AE [h]	[redacted]	NR	NR	759 (89.0)	718 (82.2)
AE that occurred during the intervention period	NR	119 (90.8)	113 (90.4)	NR	NR

Source: Partly reproduced from CS Table 13 and CS Appendix Table 55, with additional information about deaths considered to be related to the study treatment sourced from the TRAILBLAZER-ALZ clinical study report.
AE(s), adverse event(s); NR, not reported; SAE, serious adverse event; TB, TRAILBLAZER-ALZ trial; TB2, TRAILBLAZER-ALZ 2 trial.
[a] CS states that participants may have been included in more than one category.
[b] These are also included in the SAE and discontinuations due to AEs categories.
[c] One death occurred in the follow-up period (i.e. after treatment completion).
[d] CS states that value has been calculated.
[e] [redacted] (CSR section 5.2.1.1).
[f] Deaths related to donanemab occurred subsequent to ARIA and the death related to placebo occurred due to arteriosclerosis.
[g] This was defined as "results in death, is life-threatening, required inpatient hospitalization or prolongation of existing hospitalization, results in persistent disability/incapacity, or based on other medical/scientific judgment" (CS Table 13).
[h] This was defined as "an untoward medical occurrence that emerges during a defined treatment period, having been absent pre-treatment, or worsens relative to the pre-treatment state, and does not necessarily have to have a causal relationship with this treatment" (CS Table 13).

Table 24 Summary of the ARIA adverse events and observations that occurred in the TRAILBLAZER-ALZ and TRAILBLAZER-ALZ 2 trials and that are reported in an integrated safety dataset

Event, No. (%)	Donanemab All, Integrated Dataset (n=2,727)	Donanemab TB (n=131)	Placebo TB (n=125)	Donanemab TB2 (n=853)	Placebo TB2 (n=874)
ARIA-E	[redacted]	36 (27.5) [a]	1 (0.8) [a]	205 (24.0) [b]	18 (2.1) [b]
ARIA-H	[redacted]	40 (30.5) [a]	9 (7.2) [a]	268 (31.4) [b]	119 (13.6) [b]
ARIA-H or ARIA-E	[redacted]	51 (38.9) [a]	10 (8.0) [a]	314 (36.8%) [b]	130 (14.9%) [b]
Asymptomatic ARIA-E	NR	28 (21.4)	0	153 (17.9)	17 (1.9)
Symptomatic ARIA-E	[redacted]	8 (6.1)	1 (0.8)	52 (6.1)	1 (0.1) [c]
Symptomatic ARIA-H	[redacted]	NR	NR	NR	NR
ARIA-E by MRI – treatment discontinuations	[redacted]	NR	NR	NR	NR
ARIA-H by MRI – treatment discontinuations	[redacted]	NR	NR	NR	NR

Source: Partly reproduced from CS Tables 14, 15 and 16, and CS Appendix Tables 56 and 57.
ARIA-E, amyloid-related imaging abnormalities of oedema/effusion; ARIA-H, amyloid-related imaging abnormalities of microhaemorrhages and hemosiderin depo; NR, not reported; TB, TRAILBLAZER-ALZ trial; TB2, TRAILBLAZER-ALZ 2 trial.
[a] Included events beyond the double-blind period and captured all possible ARIA-H based on central review of MRI studies.[63]
[b] These figures are reported in CS Table 15, which the company states in clarification responses A17(a) and A17(b) captures all possible ARIA observations (capturing MRI findings reported as adverse events and those not reported as adverse events, as well as locally-read findings of ARIA-H in rare instances that centrally-read MRIs were not available).
[c] the CS states: “One placebo-treated participant had ARIA-E during the placebo-controlled period; however, the participant developed symptoms during the long-term extension period”.

3.2.5.9.1 Specific treatment emergent adverse events, including ARIA

Rates of treatment-emergent adverse events that occurred in ≥5% of participants are reported in CS Table 14 from the integrated safety dataset and from the TRAILBLAZER-ALZ 2 trial, and CS Appendix Table 56 from the TRAILBLAZER-ALZ trials. ARIA-E was the most common adverse event that occurred in both trials, with ARIA-H also being a frequently experienced adverse event. We summarise the ARIA rates across these datasets in Table 24 and narratively here:

- In the TRAILBLAZER-ALZ trial:
  - **ARIA-E** occurred in 26.7% of the participants in the donanemab group compared with 0.8% of the participants in the placebo group.
  - **ARIA-H** events occurred in 8.4% of participants in the donanemab group compared with 3.2% of participants in the placebo group.
- In the TRAILBLAZER-ALZ 2 trial:
  - 24.0% of participants in the donanemab group had **ARIA-E** compared with 1.9% in the placebo group.
  - The rates of **ARIA-H** were 19.7% and 7.4% for donanemab and placebo, respectively.
- The integrated safety analysis provides an overall rate of:
  - **ARIA-E** of [redacted] for donanemab and,
  - a rate of **ARIA-H** of [redacted] for donanemab.
- All ARIA events based on review of MRI are shown in Table 24.

In the TRAILBLAZER-ALZ trial, 6.1% of all the participants in the donanemab group had symptomatic ARIA-E compared with 0.8% of all those in the placebo group. The CS reports that most of the cases of ARIA-E in this trial happened at or before week 12 of the treatment period (CS Appendix I.1.2). The CS reports that two participants in the TRAILBLAZER-ALZ trial were hospitalised due to serious symptomatic ARIA-E, with symptoms resolving over a mean period of 18 weeks.

The CS also reports that most of the ARIA-E events in the donanemab group in TRAILBLAZER-ALZ 2 were mild to moderate in severity (93.1%), compared with all (100%) being of this severity in the placebo group. The trial CSR reports that [redacted] participants ([redacted]) in the donanemab group had ARIA-E that was classed as a serious adverse event, compared to [redacted] in the placebo group (CSR Table AACI.5.26).[31] In total, [redacted] participants treated with donanemab had serious adverse events that were attributable to ARIA (of any type),

with [redacted] reported in placebo participants (CSR section 5.2.1.4.1.1). The CS states that 52 participants (6.1%) in the donanemab group had symptomatic ARIA-E events compared to one participant (0.1%) in the placebo group. Hospitalisations due to ARIA are not reported in the CS or CSR for the TRAILBLAZER-ALZ 2 trial.

We note that Association of British Neurologists submission for this appraisal states that the outcomes for people who develop symptomatic ARIA have not been published.

Other adverse events for which rates appeared to differ between treatment groups were:

- infusion-related reactions, occurring in:
  - 7.6% of participants in the donanemab group compared with none in the TRAILBLAZER-ALZ trial, and
  - 8.7% of participants in the donanemab arm compared with 0.5% in the placebo group in TRAILBLAZER-ALZ 2.
- Superficial siderosis of central nervous system, which is a type of ARIA-H, occurring in:
  - 13.7% of participants in the donanemab group compared with 3.2% in the TRAILBLAZER-ALZ trial, and
  - 6.8% of participants in the donanemab group compared with 1.1% in the placebo arm in TRAILBLAZER-ALZ 2.

3.2.5.9.2 ARIA adverse events by APOE ε4 allele status

CS section B.2.9 provides a summary of ARIA-E adverse events in the TRAILBLAZER-ALZ 2 trial and the integrated safety dataset by APOE ε4 allele status. Similar data for TRAILBLAZER-ALZ are provided in CS Appendix Table 57. We have summarised these data in Table 25. As the table shows:

- proportionally more homozygous carriers in the donanemab groups had ARIA-E than noncarrier and heterozygous carriers in the donanemab groups, and
- the rates of ARIA-E in heterozygous carriers treated with donanemab were proportionally higher than those in non-carriers and proportionally lower than in homozygous carriers both treated with donanemab.

CS section B.2.9 also reports that, in the integrated safety dataset, the rate of symptomatic ARIA-E was highest in homozygous carriers treated with donanemab ([redacted]). Homozygous carriers treated with donanemab also had the highest rate of serious ARIA-E ([redacted]).

Table 25 Summary of the ARIA-E adverse events that occurred in the TRAILBLAZER-ALZ and TRAILBLAZER-ALZ 2 trials and that are reported in an integrated safety dataset by APOE ε4 allele status

APOE ε4 allele status, n/total N (%)	Donanemab All, Integrated Dataset (n=2,727)	Donanemab TB [a] (n=131)	Placebo TB [a] (n=125)	Donanemab TB2 (n=853)	Placebo TB2 (n=874)
Noncarrier	[redacted] [b]	4/36 (11.1%)	0/32 (0%)	40/255 (15.7)	2/250 (0.8)
Heterozygous carrier	[redacted] [b]	21/70 (30%)	0/64 (0%)	103/452 (22.8)	9/474 (1.9)
Homozygous carrier	[redacted] [b]	11/25 (44.0%)	1/28 (3.6%)	58/143 (40.6)	5/146 3.4)

Source: Partly reproduced from CS section B.2.9 and CS Table 15.
APOE, Apolipoprotein E genotype; ARIA-E, amyloid-related imaging abnormalities of oedema/effusion; TB2, TRAILBLAZER-ALZ 2 trial.
[a] Results for APOE genotype from TRAILBLAZER-ALZ are provided in CS Appendix Table 57, and used by the EAG to calculate percentages for the non-carrier, heterozygous carrier and homozygous carrier groupings.
[b] Numerators and denominators were not provided in the CS.

One of our clinical experts advised us that due to the risk of ARIA side effects in homozygous carriers of the APOE ε4 allele, these patients should probably not be treated with donanemab. The expert commented that they would likely still treat heterozygous carriers with donanemab. They commented that the potential risks and benefits of treatment would need to be clearly explained to heterozygous carriers and their families, and some of these patients may decide not to receive treatment. As outlined in section 2.2.1.4, APOE ε4 allele status is not currently tested in clinical practice, and thus one of our experts commented that this is an area that has resource and infrastructure implications. We raise the impact of APOE ε4 allele status as a key issue (Key Issue 5).

3.2.6 Pairwise meta-analysis of intervention studies

Although there are two placebo-controlled trials of donanemab in a relevant population for this appraisal the company do not present any meta-analyses of outcomes from these two trials. We asked the company to provide their rationale for not conducting meta-analysis (clarification question A18a) and in response the company stated that heterogeneity between the studies (particularly in terms of the trial populations and study design differences) would limit the feasibility and validity of a meta-analysis. We were already

aware of the slight differences between the phase 2 TRAILBLAZER-ALZ and phase 3 TRAILBLAZER-ALZ 3 study (discussed in section 3.2.1) and were mindful that some heterogeneity would be present. Nevertheless, we believe it would be useful to obtain a hazard ratio of disease progression based on both trials for the iADRS and CDR-SB outcomes to use in the economic model as an additional scenario analysis. We asked the company to conduct meta-analyses for these two outcomes and add an option to use the results from the meta-analyses in the economic model (clarification question A18b and c). However, based on the company's response to clarification question A18a, the company declined to do these meta-analyses. We raise this as a key issue (Key Issue 3).

3.3 Additional work on clinical effectiveness undertaken by the EAG

We are not able to undertake meta-analyses to provide HRs that could be used in the model because the appropriate data are not available within the CS or CSR for the TRAILBLAZER-ALZ trial.

3.4 Conclusions on the clinical effectiveness evidence

The company's decision problem matches the NICE scope aside from the following exceptions:

- For people with MCI the company's decision problem permits the comparator of non-pharmacological therapy to be received either alone or in combination with an acetylcholinesterase inhibitor or memantine. The use of acetylcholinesterase inhibitors in people with MCI due to Alzheimer's disease and the use of memantine in people with either MCI or mild dementia due to Alzheimer's disease is outside the recommendations of NICE NG97.[10]
- The economic analysis does not fully adhere to the NICE reference case (specifically the estimation of utilities and health care costs, see section 4.2.1)

The company's key evidence for the efficacy and safety of donanemab comes from their placebo-controlled phase 3 trial TRAILBLAZER-ALZ 2 (donanemab n=860, placebo n=876). We have presented data from the company's phase 2 trial TRAILBLAZER-ALZ alongside that for TRAILBLAZER ALZ 2 in our report because we believe there should be the option in the economic model to draw on the combined clinical effectiveness data from these trials (donanemab n=131, placebo n=126). In both trials, receipt of symptomatic treatments (e.g. acetylcholinesterase inhibitors or memantine) was permitted and both trials report final efficacy and adverse event assessments at week 76. One further trial, TRAILBLAZER-ALZ 4, a head-to-head RCT of donanemab versus aducanumab in people with early symptomatic

Alzheimer's disease is out of scope but contributes data to the integrated safety set for people who received donanemab.

The chief difference in the participants enrolled in the two trials was that people with high tau levels were excluded from TRAILBLAZER-ALZ but could be enrolled in TRAILBLAZER-ALZ 2. TRAILBLAZER-ALZ 2 was slightly enriched for a higher tau population due to the exclusion of people with no to very low tau. However, the company does not anticipate that tau pathology will need to be identified to determine whether a patient is eligible for donanemab treatment in clinical practice. Therefore, although the TRAILBLAZER-ALZ 2 participants are likely a better representation of the participants who could be treated with donanemab in clinical practice (because some people will have high tau levels), the TRAILBLAZER-ALZ participants would also be eligible for treatment.

The participants in the TRAILBLAZER-ALZ 2 RCT (and probably those in the TRAILBLAZER-ALZ trial) differed from people with either MCI or mild dementia treated within the NHS in the use of acetylcholinesterase inhibitors and memantine in participants with MCI and the use of memantine for people with mild dementia due to Alzheimer's disease which was higher than estimated in UK clinical practice (Key Issue 1).

We judged both the RCTs to be at a high risk of bias for the key secondary outcome of risk of participants progressing on the CDR-SB at week 76 (this result from the TRAILBLAZER-ALZ 2 trial informs the economic model) and we also judged that there were some concerns about attrition bias in both trials and reporting bias in relation to the TRAILBLAZER-ALZ trial. As these concerns raise the potential for the hazard ratio that informs the economic model to be biased, we raise this as one of our key issues (Key Issue 4).

The primary outcome of both the trials was the iADRS change from baseline to 76 weeks but it is the key secondary outcome of CDR-SB from the phase 3 TRAILBLAZER-ALZ 2 RCT that is the measure of treatment effect in the economic model. From baseline to 76 weeks there was a smaller reduction in iADRS scores in the donanemab arm of both trials than in the placebo arm: least squares mean difference versus placebo for TRAILBLAZER-ALZ: 3.20 (95% CI 0.12 to 6.27; p = 0.04); and for TRAILBLAZER-ALZ-2: 2.92 (95% CI 1.51 to 4.33, p<0.001). The calculated slowing of clinical progression at 76 weeks was 31.8% in the TRAILBLAZER-ALZ trial and 22.3% in the TRAILBLAZER-ALZ 2 trial. Two different assumptions about missing data were tested for the analysis of TRAILBLAZER-ALZ 2 (in the ITT population) which led to either a [redacted] (under the missing at random assumption) or a [redacted] (under the missing not at random assumption) least-squares mean change difference than for the primary analysis conducted on the mITT population). For the CDR-

SB from baseline to 76 weeks the least squares mean difference versus placebo were in favour of donanemab (TRAILBLAZER-ALZ: -0.36 (95% CI −0.83 to 0.12; p=0.139); TRAILBLAZER-ALZ-2: −0.70 (95% CI −0.95 to −0.45; p<0.001). The calculated slowing of clinical progression was 22.8% in the TRAILBLAZER-ALZ trial and 28.9% in the TRAILBLAZER-ALZ 2 trial. The sensitivity analyses conducted for the assumptions of missing data in the TRAILBLAZER-ALZ 2 (ITT population) displayed a similar pattern to those for the iADRS outcome.

The company used a hazard ratio of disease progression based on the CDR-SB outcome as a measure of treatment effect in the model (HR 0.62, 95% CI 0.52 to 0.75) (i.e. a 38% lower risk of progression based on the CDR-SB). We acknowledge that the CDR-SB was not the primary outcome of the trial, but we believe its use in the model is appropriate. However, we asked the company to provide the hazard ratio of disease progression based on the iADRS primary outcome (HR 0.700, 95% CI 0.582 to 0.842) so that we could use this in the economic model for scenario analyses (section 6.3) (Key Issue 2).

Results for other cognitive and functional impairment outcomes that were secondary outcomes and results from alternative statistical methods used to analyse the data are mixed. In the TRAILBLAZER-ALZ study the CDR-SB was the first secondary outcome tested in the pre-defined testing strategy and, because there was no significant difference between the trial arms, p-values presented for the remaining secondary outcomes must be considered nominal. In the TRAILBLAZER-ALZ 2 trial all p-values vs placebo indicate a statistically significant difference in favour of donanemab. Overall, in TRAILBLAZER-ALZ the calculated percentage of reduction values for the for five measures of cognitive and functional impairment (iADRS, CDR-SB, ADCS-iADL, ADAS Cog13 and MMSE) ranged from [redacted]% to [redacted]% and in TRAILBLAZER-ALZ 2 from 14.8% to 28.9% (this range includes results from both statistical methods used). The company also present results from time-based analyses for the TRAILBLAZER-ALZ 2 RCT. Donanemab delayed disease progression by 1.38 months (95% CI 0.46 to 2.3) by the iADRS measure and by 5.44 months (95% CI 3.90 to 6.98) using the CDR-SB measure over the 76-week trial period.

In both trials the proportion of participants with amyloid clearance at 76 weeks was much higher in the donanemab trial arms than in the placebo trial arms which was to be expected because donanemab targets a form of beta-amyloid that is only present in amyloid plaques.

The Quality of Life in Alzheimer's Disease (QoL-AD) questionnaire was used to measure HRQoL in a subset of patients and their caregivers in the TRAILBLAZER-ALZ 2 RCT the

LSM change in QoL-AD score at 76 weeks was not statistically significant for either patient-assessed or proxy-assessed QoL-AD.

Three subgroups (APOE ε4 gene carrier status, people with MCI due to Alzheimer's disease, and people with mild dementia due to Alzheimer's disease) were specified in the NICE scope as being subgroups of interest for this appraisal and the CS provides results for these subgroups from the TRAILBLAZER-ALZ 2 trial. The adjusted mean differences from placebo for all these subgroups favoured donanemab. Analyses by APOE ε4 gene carrier status suggested a trend on both the iADRS and the CDR-SB measures for a greater adjusted mean difference from placebo and slowing of disease progression at 76 weeks for noncarriers in comparison to people heterozygous for APOE ε4, with people homozygous for APOE ε4 having the smallest adjusted mean difference from placebo and slowing of disease progression. However, we are conscious that participant numbers are lowest for the homozygous for APOE ε4 subgroup and consequently the results are subject to greater uncertainty than for noncarriers or heterozygotes (Key Issue 5). Similarly, although the adjusted mean differences between groups for participants with MCI at baseline were numerically smaller than for those with mild dementia the MCI subgroup size was the smallest so the MCI results were more uncertain. Also, in terms of percentage slowing of disease progression, this was greater for the MCI subgroup than the mild AD subgroup for the iADRS measure and very similar to the mild AD subgroup for the CDR-SB measure.

Adverse event data are presented for participants from the TRAILBLAZER-ALZ and TRAILBLAZER-ALZ 2 trials and also from an integrated safety dataset that included the donanemab cohort from the TRAILBLAZER-ALZ 4 trial. In the TRAILBLAZER-ALZ and TRAILBLAZER-ALZ 2 trials the overall rates of adverse events were similar but rates of discontinuations due to adverse events (from study or from treatment) were proportionally higher among participants who received donanemab than among those who received placebo. In the integrated safety analysis, five deaths were considered to be related to donanemab treatment, representing a death rate of 0.2%.

Of particular concern is the incidence of ARIA events (some of which were designated adverse events) because the three deaths in TRAILBLAZER-ALZ 2 that were considered to be related to study treatment all occurred after ARIA events. ARIA-E was the most common treatment-emergent adverse event that occurred in either the TRAILBLAZER-ALZ or the TRAILBLAZER-ALZ 2 trial (26.7% or 24.0% in the donanemab arms of the two trials respectively compared to 0.8% or 1.9% in the placebo arms). ARIA-H events were also a frequently experienced event (8.4% or 19.7% in the donanemab arms of the two trials

respectively compared to 3.2% or 7.4% in the placebo arms). The integrated safety analysis for donanemab treated patients only gave an overall rate of [redacted]% for ARIA-E and [redacted]% for ARIA-H. In TRAILBLAZER-ALZ 2 most ARIA-E events were described as mild to moderate in severity (93.1%) but [redacted] participants ([redacted]%) who received donanemab had an ARIA-E that was classed as a serious adverse event (in the placebo group [redacted] had ARIA-E classed as a serious adverse event). The company report ARIA adverse events by APOE ε4 allele status for the TRAILBLAZER-ALZ and TRAILBLAZER-ALZ 2 trials and for the integrated safety dataset. Proportionally more homozygous carriers in the donanemab groups had ARIA-E than heterozygous carriers and noncarrier subgroups in the TRAILBLAZER-ALZ and TRAILBLAZER-ALZ 2 trials [redacted]. In the integrated dataset for people treated with donanemab, the rate of symptomatic ARIA-E was highest in homozygous carriers ([redacted]%) and this group also had the highest rate of serious ARIA-E ([redacted]%). One of our clinical experts thought homozygous carriers of the APOE ε4 allele should probably not be treated with donanemab because of the risk of ARIA side effects. Prospective patients will need to be tested for the APOE ε4 allele (which has cost and resource implications) and be counselled about the result. We raise the impact of the APOE ε4 allele as one of our key issues (Key Issue 5).

The company did not present any meta-analyses from their two placebo-controlled trials of donanemab. We believe it would be useful to obtain a hazard ratio of disease progression based on both trials for the iADRS and CDR-SB outcomes to use in the economic model as an additional scenario analysis (Key Issue 3).

4 COST EFFECTIVENESS

4.1 EAG comment on company's review of cost-effectiveness evidence

The company reports their economic search strategy in CS section B.3.1 and CS Appendix E. They conducted four separate systematic literature reviews for economic evaluations, utility evidence, healthcare resource use and indirect cost evidence, and direct cost evidence to inform the cost-effectiveness model of donanemab for the treatment of early symptomatic Alzheimer's disease (CS Appendix E Table 10). They share a subdivided PICO, but the search strategies are all reported separately. All the searches are quite recent and consist of an original search on 12th October 2022 and an update search on 4th September 2023, although only the original search strings were reported. A date limit for the searches from 2012 was used. CS Appendix E Table 11 presents the inclusion and exclusion criteria for all the four systematic literature reviews.

The company provided a list of eight included studies: four cost-utility analyses for approved Alzheimer's disease treatments and emerging therapies from the UK perspective and four economic model frameworks based on hypothetical new treatments for Alzheimer's disease from the UK perspective. In response to clarification question B1, the company provided the full list of included and excluded published cost-effectiveness studies. We note that the study by Ross et al.,[69] which estimated the cost-effectiveness of aducanumab and donanemab compared to standard of care for early Alzheimer's disease in the US, is listed as an included study but was not mentioned in the CS. The study by Lin et al.[70] was not included and was not mentioned in the CS. Lin et al. is a draft evidence report for the Institute for Clinical and Economic Review which estimated the lifetime cost-effectiveness of lecanemab and donanemab in addition to supportive care compared to supportive care alone for early Alzheimer's disease in the US. We note that on January 19th 2023, Eli Lilly announced a Complete Response Letter for accelerated approval of donanemab and therefore, the Institute for Clinical and Economic Review has removed donanemab from this assessment (https://icer.org/assessment/alzheimers-disease-2022/#timeline).

We consider that both Ross et al.[69] and Lin et al.[70] should have been mentioned in the CS as they directly address the decision problem relevant to this submission. Although we acknowledge that certain parameters of these studies (particularly the costs) are not generalisable to the English setting as they are collected from the US perspective, several other model inputs and model assumptions may be of relevance to the current appraisal. There are two caveats about the Ross study that we would like to note: the efficacy inputs for donanemab come from the small phase 2 TRAILBLAZER-ALZ trial and it is not explicit

what assumptions are used in the cost-effectiveness model regarding extrapolation of the treatment effect beyond the trial horizon. We also note that phase 2 TRAILBLAZER-ALZ data were used in the cost-effectiveness model by Lin et al. Table 26 shows some of the assumptions applied in the cost-effectiveness model developed by Lin et al. which we consider relevant for the current appraisal. For instance, Lin et al. assumed that the treatment effect was maintained while amyloid remained cleared, however the duration over which the treatment effect was retained is not stated. Table 27 shows a summary of the model structures and main results of the Ross and Lin studies while Appendix 3 Table 53 shows all the relevant model inputs for these studies. We are not aware of any additional cost-effectiveness studies that have been missed by the company.

Table 26 Model assumptions in the cost-effectiveness study by Lin et al.[70]

Assumptions
Patients were assumed to stop treatment with donanemab if they reach amyloid clearance or moderate Alzheimer's disease dementia.
Donanemab's effectiveness was assumed to be equivalent to lecanemab's due to lack of evidence of the effectiveness of donanemab in slowing disease progression to the next dementia stage.
For donanemab, no treatment effect was assumed once a patient reaches moderate Alzheimer's disease dementia.
Treatment effect was assumed to be maintained after stopping treatment with donanemab while amyloid remains cleared.
Patients who had previously stopped treatment due to amyloid clearance were assumed to restart treatment with donanemab for a fixed duration of 6 months once amyloid was detected and if they had not reached moderate Alzheimer's disease dementia.
The ARIA events and its consequences on quality of life and costs were modelled in the first year of treatment.
Only one caregiver per patient was considered (the primary caregiver).

Source: Lin et al. 2022[70]
ARIA, amyloid-related imaging abnormalities.

Table 27 Model structure and main results of the cost-effectiveness studies by Ross et al. [69] and Lin et al. [70]

Characteristics	Ross et al. [69]	Lin et al. [70]
Model structure	State transition model with 1-month cycle length, categorised by age and AD clinical stage (MCI, Mild, Moderate and Severe).	Markov model with 1-year cycle length, comprised of five health states: MCI due to AD, mild AD, moderate AD, severe AD and death.
Results		
LYs	-	Supportive care: 5.53 Donanemab: 5.96 Incremental: 0.43
QALYs	Standard of care: 4.948 Donanemab: 5.356 Incremental: 0.408	Supportive care: 2.89 Donanemab: 3.38 Incremental: 0.49
Costs	Standard of care: $118,000 Donanemab: $196,700 Incremental: $78,700	Supportive care: $339,000 Donanemab: $405,000 Incremental: $66,000
ICER for donanemab versus comparator	$193,000/QALY	$139,000/QALY

Source: Ross et al. 2022[69] and Lin et al. 2022 [70]
AD, Alzheimer disease; ICER; incremental cost-effectiveness ratio; MCI, mild cognitive impairment; QALYs, quality adjusted life years.

EAG comment on company's review of cost-effectiveness evidence

The company's searches are well constructed and use a very comprehensive range of appropriate terms. The company searched a good range of sources. In our opinion, the studies by Ross et al.[69] and Lin et al.[70] are relevant for the current appraisal and should have been described in the CS.

4.2 Summary and critique of the company's submitted economic evaluation by the EAG

The company developed a de novo economic model to assess the cost-effectiveness of donanemab in the treatment of patients with MCI due to Alzheimer's disease or mild Alzheimer's disease dementia and evidence of amyloid beta pathology.

4.2.1 NICE reference case checklist

The company's economic model fulfils the requirements of NICE's reference case (Table 28), except for the estimation of utilities and health care costs where:

- The time trade off method has been used to derive preference values for caregivers (section 4.2.10.2.2).
- General population participants completed the time trade off interviews for caregiver utilities, by imagining they were caregivers of patients with MCI or Alzheimer's disease dementia (section 4.2.10.2.2).
- Different country value sets were combined in a meta-analysis which was used to estimate the patients' utility values (section 4.2.10.2.1).
- The health care costs were obtained from the PSSRU report,[71] which included unpaid care costs (section 4.2.11.5).

Table 28 NICE reference case checklist

Element of health technology assessment	Reference case	EAG comment on company's submission
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	Yes
Perspective on costs	NHS and PSS	Yes
Type of economic evaluation	Cost–utility analysis with fully incremental analysis	Yes
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	Yes
Synthesis of evidence on health effects	Based on systematic review	Yes

Element of health technology assessment	Reference case	EAG comment on company's submission
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of health-related quality of life in adults.	EQ-5D used for patient utilities and TTO vignettes used for caregiver utilities
Source of data for measurement of health-related quality of life	Reported directly by patients and/or carers	No, as the caregiver utilities were reported by general population participants
Source of preference data for valuation of changes in health-related quality of life	Representative sample of the UK population	No, different country-specific value sets were combined in a meta-analysis
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Yes, donanemab does not meet the criteria for the NICE severity modifier (see response to clarification question B33)
Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS	No, as the health care costs include unpaid care costs
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	Yes

Source: EAG assessment based on the company submission.
CS, company submission; EAG, External Assessment Group; NHS, National Health Service; NICE, The National Institute for Health and Care Excellence; PSS, Personal Social Services; QALY, quality adjusted life-year; TTO, time trade-off; UK, United Kingdom.

4.2.2 Model structure

The company developed a de novo cost-effectiveness model, which is described in CS section B.3.1.3. The model parameters are presented in CS sections B.3.2 to B.3.4, the base case inputs in CS Table 47 and the model assumptions in CS Table 48. The company developed a Markov cohort state transition model with five mutually exclusive health states, including MCI due to Alzheimer's disease, mild Alzheimer's disease dementia, moderate Alzheimer's disease dementia, severe Alzheimer's disease dementia, and death (Figure 2

below). Patients start the model either on the MCI due to Alzheimer's disease or mild Alzheimer's disease dementia health state, where treatment with donanemab is initiated. A six-month cycle length was adopted, and half-cycle correction applied. At each cycle in the model:

- Patients may remain in their current health state or progress to a more severe health state, according to transition probabilities which are discussed in sections 4.2.6 and 4.2.9.
- Patients in all health states, except the severe Alzheimer's disease dementia health state and death, may continue treatment with donanemab or stop treatment for one of the following reasons (fixed treatment duration, amyloid clearance, progression to the severe health state and adverse events), which are further discussed in section 4.2.4.
- Patients in all health states can transition to the death health state due to all-cause and disease-specific mortality, further discussed in section 4.2.8.
- Patients could be in a community or residential care setting (section 4.2.7).

Although the model structure diagram does not show the possibility of treatment within the moderate health state, we believe this is a typo as progression to moderate disease is not listed as a stopping rule in the CS (see section 4.2.4).

Before entering the model, patients with MCI due to Alzheimer's disease or mild Alzheimer's disease dementia are screened for treatment eligibility (i.e., amyloid positivity) and therefore the screening costs are included in the model base case (see Table 39 in section 4.2.11.4 below).

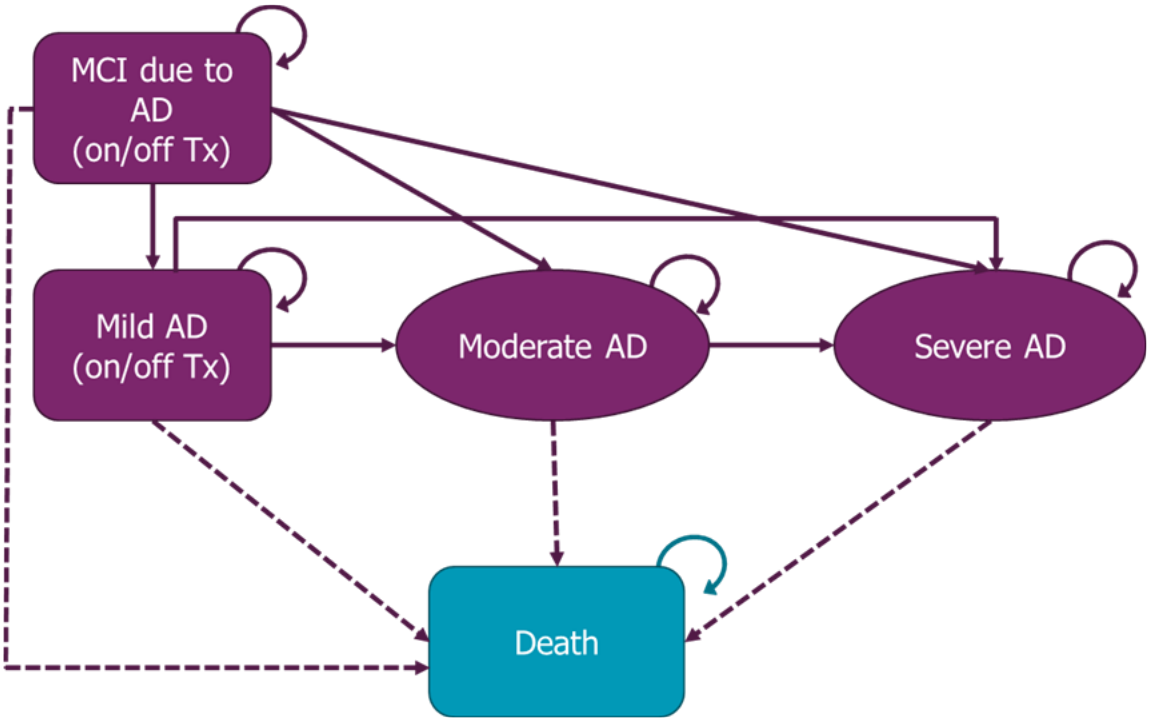

Figure 2 Model structure

Source: Reproduced from CS Figure 13
AD, Alzheimer disease; MCI, mild cognitive impairment; Tx, treatment.

EAG comment on model structure

The EAG considers the model structure to be appropriate for this condition, and in line with previous cost-effectiveness studies for amyloid-targeting therapies.[69; 70; 72; 73] The company adopted a six-month cycle length as this is the time interval for the assessment of amyloid clearance in the TRAILBLAZER-ALZ 2 trial. Although previous cost-effectiveness studies applied a different cycle length (one month or one year),[69; 70; 72; 73] we do not consider that this affects the model outcomes.

4.2.3 Population

The population considered in the company model is described in CS section B.3.1.2 and consists of patients with MCI due to Alzheimer's disease and mild Alzheimer's disease dementia. This is aligned with the population defined in the NICE scope and the modified-ITT population in the TRAILBLAZER-ALZ 2 trial. The company also states that the population is reflective of the expected marketing authorisation for donanemab.

The baseline characteristics of the model population are presented in CS section B.3.2.1 (CS Table 19). These were taken from the TRAILBLAZER-ALZ 2 trial.[30] Table 29 shows the model inputs for baseline age and gender characteristics as well as the distribution of

patients across MCI due to Alzheimer's disease and mild Alzheimer's disease dementia. The clinical experts advising the EAG agree that these are representative of the patients who may receive donanemab treatment in clinical practice. We note that the patients were categorised as MCI due to Alzheimer's disease or mild Alzheimer's disease dementia according to the MMSE score. The company assumed that all patients start the model in the community setting and our clinical experts agreed with this assumption as the number of patients with MCI due to Alzheimer's disease or mild Alzheimer's disease dementia in residential care is minimal.

Table 29 Baseline characteristics of the population

	MCI due to AD	Mild AD dementia
Distribution of patients across MCI due to AD and mild AD dementia (MMSE), %	20.4%	79.6%
Proportion of females, %	49.6%	57.0%
Proportion in residential care, %	0%	0%
Age, years (SD)	72.81 (5.79)	72.76 (6.23)

Source: Partly reproduced from CS Table 19 and section B.3.2.1.
AD, Alzheimer disease; MCI, mild cognitive impairment; MMSE, Mini-Mental State Exam; SD, standard deviation.

The CS also includes the baseline characteristics of caregivers, as the mean age and gender distribution of caregivers informs the age adjustment of utility values for caregivers over time (CS section B.3.2.1). Both spouse caregivers and adult child caregivers were incorporated into the model, as the company assumed different quality of life estimates according to the relationship of the caregiver to the patient (for further details, please read section 4.2.10.2.2). Table 30 shows the distribution of spouse and child caregivers and their baseline characteristics, which are based on the GERAS study and considered by our clinical experts to be reasonably representative of the caregivers of patients who may receive donanemab treatment in clinical practice.[74] The number of caregivers per patient in the UK (1.8) was also obtained from the GERAS study.[75] We discuss the number of caregivers per patient in more detail in section 4.2.10.2.2, but our preference is to model disutility for the primary caregiver only even though we recognise that secondary caregivers may also experience a decrement in their quality of life. Therefore, we changed the number of caregivers per patient to one in the EAG base case.

Table 30 Baseline characteristics of caregivers from GERAS study[74; 75]

	Model inputs
Proportion of child caregivers, %	29.1%
Mean age of child caregivers, years	54.1 ± 8.1
Proportion of male child caregivers, %	25.4%
Mean age of spouse caregivers, years	73.4 ± 8.0
Proportion of male spouse caregivers, %	41.2%
Number of caregivers per patient	1.8

Source: Adapted from CS Table 20 and the economic model.

4.2.3.1 GERAS study

We are going to add a brief description of the GERAS study[76] here because it reports relevant data to inform several model inputs across this appraisal. The GERAS study is an 18-month prospective, multi-center, naturalistic, observational cohort study. Its main objective is to evaluate costs and resource use associated with Alzheimer's disease patients and caregivers in France, Germany and the UK. HRQoL was evaluated in both patients and caregivers using the EQ-5D instrument. Physicians, mainly from specialist secondary care clinics ('memory clinics'), enrolled community-dwelling patients from October 2010 to September 2011 who were aged at least 55 years old, diagnosed with probable Alzheimer's disease, defined according to the National Institute of Neurological and Communicative Disorders, and Stroke and Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria, and with MMSE score ≤ 26. Patients were required to have a primary caregiver, defined as an informal carer who normally takes most responsibility for the daily decisions and provision of home care for the patient, willing to participate in the study and be responsible for the patient for at least six months of the year. Ninety-four investigators were involved in this study, most were specialists: 34.8% were psychiatrists, 32.6% were neurologists and 30.3% were geriatricians. In the UK, 78.9% were psychiatrists and 15.8% were geriatricians. Around 35% of the patients participating in the study were from the UK. None of our clinical experts were aware of any limitations of the GERAS study that could affect its use in the current economic model. However, one clinical expert indicated that he was unclear from where the GERAS study patients were recruited and whether they were representative of patients with MCI and mild Alzheimer's disease dementia in NHS memory clinics.

EAG comment on model population

The patient population included in the cost-effectiveness analysis aligns with the NICE scope, expected marketing authorisation and the modified-ITT population of the TRAILBLAZER-ALZ 2 trial. The patient and caregiver baseline characteristics, based on the TRAILBLAZER-ALZ 2 trial and GERAS study, respectively, are reflective of clinical practice. We consider that only the primary caregiver of patients with Alzheimer's disease should be included in the model and made this assumption in our base case.

4.2.4 Interventions and comparators

CS sections B.3.1.4 and B.1.3.4 describe the intervention and comparators. The economic model compares donanemab plus established clinical management (referred to as BSC) versus BSC only.

Donanemab is administered via intravenous infusion at the recommended dose of 700mg every four weeks, titrated up to 1400mg from the fourth dose onwards. The infusion for donanemab lasts 30 minutes and, patients should be observed for another 30 minutes or more after the infusion. The company's assumptions around treatment duration are the following:

- 90% of patients have treatment with donanemab for a fixed duration of 18 months.
- 10% of patients have treatment with donanemab until reaching amyloid clearance for up to a maximum of 18 months.
- Patients also stop treatment if they have progressed to the severe Alzheimer's disease dementia health state or if they had adverse events that would lead to discontinuation (negative stopping rules).

A PET scan is needed to confirm if a patient reached amyloid clearance. However, the PET scan infrastructure in the UK is currently limited as stated by the company and advised by our clinical experts. The clinical experts advising the EAG also added that the current infrastructure might be sufficient to confirm patient's eligibility to receive treatment with donanemab but that it is unlikely that patients will be monitored with PET scans to confirm amyloid clearance during treatment. For that reason and based on the limited capacity of the UK health system, we assume that all patients have a fixed treatment duration with donanemab of 18 months in the EAG base case, apart from those who discontinue treatment due to adverse events or progression to severe dementia.

In the cost-effectiveness model conducted by Lin et al., patients were assumed to stop treatment once they progressed to the moderate Alzheimer's disease dementia health state (see Table 26 above). Expert opinion to the EAG indicated that progression to moderate disease is not expected to be a stopping criterion. Thus, we agree with the company's assumption that patients stop treatment if they have progressed to the severe rather than the moderate Alzheimer's disease dementia health state.

The model assumes that standard of care symptomatic treatments for Alzheimer's disease can be administered alongside donanemab. Our experts also expect that symptomatic treatment as per standard of care would continue to be given to patients on donanemab as they have different mechanisms of action and therefore benefits of their own.

The comparator is established clinical management (BSC) without donanemab. This includes non-pharmacological management for patients across all health states and off-label symptomatic treatment with acetylcholinesterase inhibitors for patients with MCI due to Alzheimer's disease and acetylcholinesterase inhibitors and memantine for patients with mild, moderate or severe dementia due to Alzheimer's disease (see section 2.3 for further details).

EAG comment on intervention and comparators

The intervention and comparator in the economic model are broadly consistent with the NICE scope. We assume that all patients receive donanemab for a fixed duration period of 18 months because of the limited PET scan infrastructure needed to monitor patients for amyloid clearance.

4.2.5 Perspective, time horizon and discounting

The perspective of the analysis is the National Health Service (NHS) and Personal Social Services (PSS) in England and the discounting rate for costs and outcomes is 3.5% per year, in line with the NICE reference case.[77] A lifetime time horizon was applied.

EAG comment on perspective, time horizon and discounting

The company uses the recommended perspective and discounting rates and an appropriate time horizon, which are all in line with NICE guidelines.[77]

4.2.6 Natural history of disease progression

The natural history of Alzheimer's disease progression is discussed in CS section B.3.2.3, with further information in the company's response to clarification questions B15 and B16.

4.2.6.1 Source of data

Transition probabilities between the model health states of MCI due to Alzheimer's disease, mild, moderate, and severe Alzheimer's disease are based on the National Alzheimer's Coordinating Centre Uniform Dataset (NACC UDS).[78] This contains longitudinal clinical registry data for over 50,000 patients recruited since 2005, contributed by 42 US research centres (https://naccdata.org). Since 2015, some research centres have provided ante-mortem biomarker data (including amyloid levels from PET scans and CSF samples), which improves identification of individuals with cognitive impairment related to Alzheimer's disease. Potashman et al. [79] reported an analysis of NACC UDS data from 2005 to 2017, stratified in 'incident' (n=3291) and 'prevalent' (n=4370) cohorts.

The company explain why they did not attempt to derive transition probabilities from the TRAILBLAZER-ALZ trials or alternative data sources (Wimo et al. 2013; Vos et al.; Wimo et al. 2020)[76 80 81] in response to clarification questions B15 and B16d, respectively. The NACC dataset is a US source and ideally the model should be informed by UK inputs where available. In response to clarification question B16c, the company argue that the transition probabilities from the US NACC UDS are generalisable to the UK clinical setting. They note that, although there are prognostic factors that are likely to differ between the countries, the key factors are accounted for in their analysis, as the sample was restricted to people with biomarker-confirmed early Alzheimer's disease, and results are adjusted for age and sex. Residual effects of other prognostic factures (e.g., cardiovascular comorbidities) are expected to be limited after the adjustment for age and sex. The EAG is not aware of any relevant UK source to inform the transition probabilities and therefore consider the use of the US NACC UDS to be acceptable.

4.2.6.2 Base case transition probabilities

The company provided a protocol detailing the methods used to estimate transition probabilities for their base case with their response to clarification questions.[82] The methods largely follow the approach of Potashman et al.[79] but were conducted with an updated NACC dataset (June 2005 and June 2023). The primary analysis, used in the company's base case, was conducted on a prevalent cohort with biomarker-confirmed early Alzheimer's disease (n=3,334), as this was expected to be more reflective of the patient population in practice than an incident cohort.

Health states were assigned on the basis of CDR-SB thresholds for MCI, mild, moderate and severe Alzheimer's disease (see clarification response document Table 17). Some adjustments were made for non-concordance between the CDR-SB score and clinician

assessment, more frequent and missing visits, and observed improvements in health state (patients with an observed improvement were retained in their previous health state). Multinomial logistic regression models were fitted to estimate the annual transition probabilities from one health state to another, conditional on the initial state, and with adjustment for time between visits, age and sex. Based on the resulting equations, mean annual transition probabilities were calculated for each pair of health states, adjusted for a mean age (73 years) and sex (55% female) to reflect the model population, see CS Table 24.

Annual transition probabilities are adjusted in the model for the cycle length by converting to an exponential rate and then converting to six-month probabilities. The probabilities for remaining in the same health state are calculated as the difference between 100% and the sum of the scaled probabilities of moving to a more severe health state. The transition matrix is re-calculated at each cycle to account for age-related mortality. Otherwise, the risks of disease progression are assumed not to change over time. Table 31 below shows the base case annual transition probabilities adjusted to exclude mortality, which is modelled separately (see section 4.2.8 below).

The clinical experts advising the EAG found the transition probabilities used in the company's base case to be reasonable. We note that the company has not provided a detailed report of the results of their NACC dataset analysis, including information about the fit of the model or results for the incident cohort.

4.2.6.3 Transition probability scenarios

The company reported a scenario analysis with transition probabilities reported by Potashman et al.,[79] who estimated annual probabilities for all Alzheimer's disease stages from asymptomatic to death defined by CDR-SB scores based on the NACC UDS records from September 2005 to December 2017. This study reported results for both incident (n=3,291) and prevalent (n=4,370) cohorts with amyloid restriction (Potashman et al. Tables 3 and 4 respectively).[79] The company chose to use data from the incident cohort in their scenario analysis because of the concerns reported by Potashman et al. that the transition probabilities from the prevalent cohort may be biased towards higher transition probabilities due to the unobserved time that patients spent in their current health state before entering the NACC. We note that the company's decision to use the incident cohort in this scenario analysis is inconsistent with their use of prevalent NACC cohort data in the company's base case.

The company adjusted the Potashman et al. results: limiting the analysis to symptomatic disease only (in line with the NICE scope); assuming that no improvement in health state is possible, by retaining patients with an observed improvement in their previous health state; and adjusting to scale the sum of probabilities for live health states to 100% (as mortality is modelled separately). We note that no patients transitioned to asymptomatic disease from mild, moderate or severe Alzheimer's disease in the Potashman incident or prevalent cohorts.

Annual transition probability estimates from the Potashman incident and prevalent cohorts are shown in Table 31, both with and without an assumption that improvement in CDR-SB health states is possible. Results are similar for the incident and prevalent cohorts and have little impact on the cost-effectiveness results (see EAG scenario analyses in Table 46). The assumption that no improvement in health state is possible has a larger impact on the ICER, as patients are estimated to spend less time in the less severe health states, which reduces estimated QALY gains. Potashman et al. suggest that the small proportions of patients with an apparent improvement based on CDR-SB scores might be due to day-to-day fluctuations and longer follow-up would be needed to clarify whether and when these patients decline again. Our clinical experts do not expect any meaningful improvement in clinical practice because of the progressive and irreversible nature of Alzheimer's disease. They suggest that the variability of assessment results may be a reason for some patients to show improvement. Or patients can be misdiagnosed with Alzheimer's disease when cognitive impairment is actually caused by a different condition (e.g., depression, hypothyroidism, or vitamin deficiency) where patients can potentially improve.

Table 31 also shows the transition probabilities estimated for the economic analyses conducted by Ross et al. and Lin et al.[69 70] Lin et al. modelled the possibility of improvement from the mild, moderate, and even the severe Alzheimer's disease dementia health states, based on the results reported by Potashman et al. The transition between the MCI and the mild health state is higher in Lin et al. and patients on MCI due to Alzheimer's disease do not transition to moderate or severe health states. The monthly transition probabilities from Ross et al. were converted to annual probabilities but they are not suitable to inform the current model given the different cycle length between the Ross model (1 month) and the current one (6 months).

EAG comment on disease progression probabilities

In the absence of a study conducted in the UK setting, we consider that the US NACC natural history disease transition probabilities from the company are plausible and

reasonably reflective of patients treated in clinical practice in England. It is appropriate to remove asymptomatic cases from the NACC data used for transition probability calculations, as this group is outside of the NICE scope for this appraisal.

On balance, the EAG consider that data for a cohort with prevalent disease should be used to calculate disease progression probabilities, because patients previously diagnosed with MCI due to Alzheimer's disease or mild Alzheimer's disease dementia would likely be suitable for treatment with donanemab if it is recommended. However, EAG scenario analyses comparing ICERs using transition probabilities estimated from prevalent and incident cohorts show little impact in the cost-effectiveness results.

The company's assumption that patients cannot experience an improvement in their disease is reasonable as it is very unlikely that a patient would improve, according to the EAG clinical experts. However, there is an argument that correcting for observed reductions in CDR-SB scores which may be due to fluctuations in symptoms, misdiagnosed or measurement error, is overly conservative, because corrections are not made for potential fluctuations or errors in the other direction.

Table 31 Annual health state transition probabilities

Health state transition	Company's NACC base case [a]	Potashman incident, no improvement [b] 79	Potashman incident, with improvement [c] 79	Potashman prevalent, no improvement [d] 79	Potashman prevalent, with improvement [e] 79	Ross et al. 2022 [f] 69	Lin et al. 2022 70
MCI to mild AD	26.6%	16.68%	16.68%	31.3%	31.3%	8%	23%
MCI to moderate AD	1.4%	5.98%	5.98%	3.8%	3.8%	-	-
MCI to severe AD	0.2%	0.21%	0.21%	0.6%	0.6%	-	-
Mild AD to MCI	-	-	3.31%	-	2.8%	-	3%
Mild to moderate AD	30.5%	34.84%	34.84%	35.6%	35.6%	18%	35%
Mild to severe AD	3.0%	4.74%	4.74%	4.6%	4.6%	-	4%
Moderate to mild AD	-	-	2.62%	-	4.0%	-	3%
Moderate to severe AD	36.0%	41.57%	41.57%	40.4%	40.4%	27%	42%
Severe to moderate AD	-	-	2.44%	-	1.5%	-	2%

Source: Produced by the EAG from the company's economic model ("Source data" sheet); Potashman et al. 2021;[79] Ross et al. 2022;[69] Lin et al. 2022.[70]
AD, Alzheimer's disease; MCI, mild cognitive impairment.
[a] From the company's base case analysis. Note these values differ from CS Table 24 because the latter includes mortality
[b] Transition probabilities from the incident cohort adjusted to remove asymptomatic patients, assuming no improvement
[c] Transition probabilities from the incident cohort adjusted to remove asymptomatic patients, improvement allowed
[d] Transition probabilities from the prevalent cohort adjusted to remove asymptomatic patients, assuming no improvement
[e] Transition probabilities from the prevalent cohort adjusted to remove asymptomatic patients, improvement allowed
[f] Monthly probabilities converted to annual probabilities using the following formula: annual probability = 1-(1-monthly probability)^(12/1)

4.2.7 Risk of residential care

Table 32 (CS Table 27) shows the annual risk of residential care used in the company's model, obtained from the study by Spackman et al.[83] This is converted to cycle probabilities for patients moving from the community to the residential care setting in the model. The company assumed that patients with MCI due to Alzheimer's disease have no risk of residential care due to limited evidence and minimal impact on the model outcomes.

Table 32 Annual probability of residential care

Disease health state	Company's base case	Lin et al. 2022 base case[70]	GERAS study, 2019[84]
MCI due to AD	0%	2.4%	-
Mild AD dementia	1.2%	3.8%	4.1%
Moderate AD dementia	3.4%	11%	8.5%
Severe AD dementia	6.6%	25.9%	10.5%

Source: Reproduced from CS Table 27; Lin et al. 2022[70] and GERAS study[84]
AD, Alzheimer's disease; MCI, mild cognitive impairment.

We also present the annual probabilities of residential care used in the cost-effectiveness model by Lin et al.[70] and the GERAS study probabilities (reported by Belger et al. 2019)[84] in Table 32. The EAG notes that Lin et al. used considerably higher annual probabilities of residential care than the company's model. However, we also note that the source for the probabilities from Lin et al. is quite old, from 1999,[85] and it is possible that the probability of moving to residential care has changed since then. The GERAS study has been previously described in section 4.2.3.1 above. We adjusted the 36-month probabilities from this study to calculate the annual probabilities showed in Table 32.[84] As the GERAS study provides the most recent estimates and includes patients from the UK, we prefer to use these probabilities in the EAG base case (section 6.2). Both our clinical experts agree that the values from the GERAS study are more suitable than the company's base case and Lin's values, although one of the experts would expect that around 15-20% of patients with severe Alzheimer's disease dementia would move to residential care per year.

EAG comment on the risk of moving to residential care

We prefer to use the annual probabilities of residential care from the GERAS study in our base case[84] as they are more recent than the company's and Lin's probabilities and also include UK patients. Our clinical experts consider the annual probability of moving to residential care from the GERAS study to be reasonable,

although one of the experts would expect a higher probability for patients in the severe health state (around 15-20%).

4.2.8 Mortality

Mortality is described in CS section B.3.2.5. The company applied a hazard ratio for mortality in patients with mild, moderate and severe Alzheimer's disease dementia relative to the general population of 2.55 (CS Table 29). This estimate was based on the Office for National Statistics 2023[86] and is the adjusted hazard ratio for mortality not involving COVID-19 in males of 65 years or older, comparing people with dementia to people without dementia in England from January 2020 to December 2022 (response to clarification questions B17a). Patients with MCI due to Alzheimer's disease were not considered to have a higher risk of mortality than the general population. Patients in the community and residential care settings were assumed to have the same mortality, although advice from our clinical experts suggests that patients in residential care are likely to suffer from more health risks and therefore to have a higher risk of mortality when compared to patients in the community setting.

The EAG notes that both published cost-effectiveness studies assessing donanemab described in section 4.1[69] [70] applied different hazard ratios for mortality according to disease severity (see Appendix 3 Table 53). Also, they both considered that patients with MCI due to Alzheimer's disease have a slightly higher risk of death than the general population (HR of 1.61 in Ross et al. and 1.82 in Lin et al.). One of our clinical experts is of the opinion that patients with MCI due to Alzheimer's disease have a higher risk of death than the general population,[87] while the other does not expect mortality of MCI patients to be different from healthy seniors.[1] A recent study using US NACC UDS data reported by Crowell et al. shows that mortality risk increases as patients' disease progresses [1] and that patients with MCI due to Alzheimer's disease had the same risk of death as cognitively normal participants. In response to clarification question B17b, the company explained that they did not vary the mortality hazard ratio by disease stage in their base case because it adds uncertainty to the model (for further details on the company's arguments, see their response in the clarification document). Anyway, the company updated the model to include the option to vary the mortality hazard ratio according to the severity of Alzheimer's disease and provided hazard ratios from the NACC dataset to inform this new option (see Table 33). We note that the company's estimates of the NACC hazard ratio of death for the mild health state is higher than for the moderate health state, which we consider to be unlikely.

Table 33 shows the hazard ratios of mortality used (a) in the company's base case, (b) in the company's new option based on the NACC dataset, (c) in the cost-effectiveness studies by Ross et al. and Lin et al., and (d) the hazard ratios estimated in the recent study by Crowell et al., which is also based on the US NACC UDS. According to the hazard ratios shown in Table 33, we consider that the values from the Crowell study for patients at age 80 years may provide a good approximation to the mortality for a population with a starting age of 73 years (the baseline age in the current model). Therefore, we applied the hazard ratios from Crowell et al. in our EAG base case (section 6.2) and explored the impact of this assumption in scenario analyses, by using alternative hazard ratios from Ross and Lin studies. The clinical experts advising the EAG are unclear on which of the estimates in Table 33 are the most representative of the English population, but they agree that the risk of death should increase with disease severity and that it is quite high in severe dementia in people at 80 years old.

Table 33 Hazard ratio of mortality compared to general population.

Health state	Company's base case (ONS)	Company's option (NACC data)	Ross et al.[69]	Lin et al.[70]	Crowell et al. (NACC data) –age 65 years[1]	Crowell et al. (NACC data) –age 80 years[1]
MCI due to AD	1	1	1.61	1.82	1	1
Mild AD dementia	2.55	1.79	2.23	2.92	6.7	2.4
Moderate AD dementia	2.55	1.75	3.10	3.85	14.8	3.1
Severe AD dementia	2.55	3.41	4.98	9.52	30.1	6.6

Source: Reproduced from CS Table 29, Ross et al. 2022,[69] Lin et al. 2022,[70] and Crowell et al. 2023.[1]
AD, Alzheimer's disease; MCI, mild cognitive impairment; NACC, National Alzheimer's Coordinating Centre.

The company applied an additional mortality risk of 0.35% to patients being treated with donanemab, calculated by dividing the total number of deaths related to treatment within the TRAILBLAZER-ALZ 2 trial by the total number of participants (3/853=0.003516) (response to clarification question B18). This was only applied once in the model at the end of the first cycle. The EAG agrees with the company's calculation and application in the model of the donanemab-specific mortality.

EAG comment on mortality

As in previous cost-effectiveness studies of donanemab, we consider it is more appropriate to use mortality hazard ratios that increase with increasing disease severity. We consider that the hazard ratios for mortality estimated by Crowell et al. are reasonable for a population with a mean age of 73 years at baseline. Therefore, we used these in the EAG base case, and explore mortality hazard ratios from alternative sources in scenario analyses. We consider that the company appropriately modelled the additional risk of death for patients treated with donanemab.

4.2.9 Treatment effectiveness and extrapolation

4.2.9.1 Treatment effect of donanemab

Treatment effect is described in CS section B.3.2.2. The treatment effect of donanemab relative to BSC was modelled by applying a hazard ratio of disease progression based on the CDR-SB measure to the underlying transition probabilities of the disease natural history (previously described in section 4.2.6 above), as in previous cost-effectiveness studies of donanemab.[69; 70] As we discussed earlier (section 3.2.2.1.1.2), the CDR-SB is a secondary outcome in the TRAILBLAZER-ALZ 2 trial and was considered by the company to be a well-established outcome measure and more widely recognised than the iADRS, the primary outcome of the TRAILBLAZER-ALZ trials. A previous cost-effectiveness study of donanemab for early Alzheimer's disease applied a hazard ratio of disease progression based on the iADRS results from the phase 2 TRAILBLAZER-ALZ trial.[69] On the contrary, in the study by Lin et al.,[70] a hazard ratio based on the CDR-SB score was applied for both donanemab and lecanemab, although it was obtained from the primary outcome results of the phase 3 trial of lecanemab.[17] The company provided more details on their rationale for choosing the CDR-SB for modelling the treatment effect in response to clarification question B5. They also added the option to use a hazard ratio based on the iADRS to the model. Section 3.2.2.1.1.6 above includes a full discussion of the EAG perspective on the use of the CDR-SB in the company's model: we are of the opinion that using the CDR-SB is appropriate. However, we consider that further input from clinical experts on this matter would be helpful and, for completeness, we tested the use of iADRS to inform the hazard ratio of disease progression in a scenario analysis.

A hazard ratio of 0.62 (95% CI 0.52-0.75) was used in the model for patients transitioning from the MCI, mild and moderate health states to more severe health states (for further

details about the company analysis of CDR-SB for the economic model, see section 3.2.5.2 above). Patients with severe Alzheimer's disease dementia were assumed to discontinue treatment and do not have any treatment benefit. The hazard ratio was estimated using a Cox proportional hazard model and the company provided evidence that the proportional hazards assumption holds as part of their response to clarification question B7, which we agree with. The hazard ratio was obtained from the TRAILBLAZER-ALZ 2 trial although we consider that the company should have conducted a meta-analysis of both TRAILBLAZER-ALZ and TRAILBLAZER-ALZ 2 trials for the clinical outcomes. This has been discussed above in section 3.2.6, and we consider that a hazard ratio combining the results of both TRAILBLAZER-ALZ trials for the iADRs and CDR-SB outcomes would provide a pertinent summary of the treatment effect of donanemab versus BSC to be used in scenario analyses or potentially in the EAG base case. However, we note that the company declined to conduct a meta-analysis in their response to clarification question A18.

EAG comment on treatment effect of donanemab

We consider the use of CDR-SB to inform treatment effect of donanemab to be appropriate. However, a combined hazard ratio based on meta-analysis of both TRAILBLAZER-ALZ studies would be useful to test in the model. We have not included the pooled CDR-SB input in the EAG base case or explored it in scenario analyses because the company declined to provide these data in response to clarification questions.

4.2.9.2 Assumptions around the duration of the treatment effect of donanemab over the time horizon of the model

Figure 3 illustrates how the company modelled the treatment effect of donanemab over the lifetime time horizon of the model. The time horizon is split into three parts: the trial period, the post-trial (medium term) period and the post-trial (long-term) period. The model assumes that (a) the full treatment effect is applied while patients receive treatment with donanemab (trial period); (b) after stopping treatment with donanemab (except if this happens due to patients progressing to the severe health state), the full treatment effect is retained until patients have reaccumulated amyloid up to a 'positive' level of >24.1 CL (post-trial medium term period); (c) and then the treatment effect is assumed to wane gradually over time until disease progression rates match those of patients who have not received treatment (post-trial long term period).

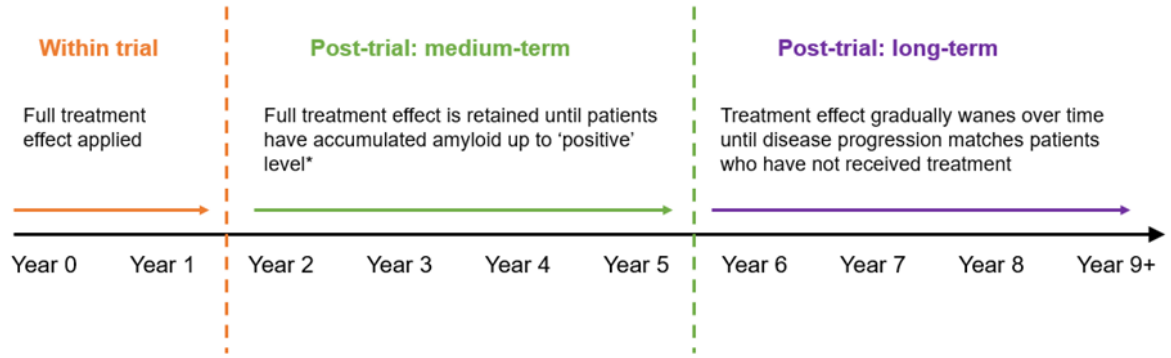

Figure 3 Approach to modelling the treatment effect over the time horizon

Source: Reproduced from CS Figure 14.

Company assumptions around the treatment effectiveness of donanemab beyond the TRAILBLAZER-ALZ 2 trial period (maximum follow-up of 18 months) are presented in Table 34 below. These were based on the relationship between amyloid levels and disease progression.

The company estimated that the time taken for a return to amyloid positivity after treatment discontinuation was 3.5 years, based on the PET-imaging amyloid plaque level at week 76 in the TRAILBLAZER-ALZ 2 trial and assuming a re-accumulation rate of 2.8 CL per year. Amyloid positivity was defined as an amyloid plaque level >24.1CL. We find the definition of amyloid positivity used in the company's base case to be reasonable but there is some uncertainty around this, and further clinical expert opinion may be needed (please see section 3.2.2.1.2). The company assumed a median amyloid plaque re-accumulation rate of 2.8 CL per year (95% CI 2.16 to 3.11), predicted by simulations in a treatment-exposure model informed by data from four donanemab clinical trials (AACD, TRAILBLAZER-ALZ 2, TRAILBLAZER-ALZ and TRAILBLAZER-EXT) (CS section B.3.2.2). Although the EAG clinical experts acknowledge the results of the treatment-exposure model simulations conducted by the company which suggest that a re-accumulation rate of 2.8 CL per year is a reasonable assumption, they are unclear about assuming that full treatment effect is retained for 3.5 years after stopping treatment as there is no long-term data available to support it.

A subgroup analysis assessing patients who achieved early amyloid clearance at six or 12 months from the TRAILBLAZER-ALZ trial indicated that these patients experienced a comparable slowing of clinical progression at week 76 as patients who continued treatment after six months, supporting the assumption that treatment effect is maintained after stopping treatment. CS Figure 18 shows the change in CDR-SB from baseline to week 76 in patients who discontinued treatment after six or 12 months due to amyloid clearance (<24.1CL)

versus patients in the placebo arm. The proportion of patients who discontinue treatment at six or 12 months due to amyloid clearance in the model is 29.7% and 36.42%, respectively. This information comes from the overall population of the TRAILBLAZER-ALZ 2 trial (CS Table 23). Furthermore, the company added that data from TRAILBLAZER-EXT phase 2 trial also suggested that the treatment effect is retained after stopping treatment with donanemab. This is a long-term trial where patients originally randomised to donanemab in TRAILBLAZER-ALZ participated in long-term follow-up visits with no treatment (CS Figure 19). However, the company acknowledge several limitations of this trial, such as a small sample size (n=25). The EAG recognise that CS Figure 18 and the results from the study by Shcherbinin et al. (in particular, eFigure 2, eTable 2) show that amyloid clearance (<24.1 CL) was maintained for a period of one year in patients who reached amyloid clearance at 24 weeks in the TRAILBLAZER-ALZ trial.[14] But we note that there is no data on treatment effect beyond the trial period.

CS Figures 15, 16 and 17 illustrate the correlation between amyloid reduction and clinical efficacy in the trial periods for amyloid targeting therapies. The company also argues that early amyloid clearance is correlated with long-term outcomes, but no evidence was provided. The clinical experts advising the EAG are unclear about the link between amyloid clearance and clinical benefit. They acknowledge that different anti-amyloid anti-body studies show an association between the magnitude of amyloid lowering and clinical benefit, but they are also aware of amyloid-PET imaging studies in elderly people with normal cognition showing that they have β-amyloid deposition in their brains at pathological levels.[88] [89] We consider that the relation between amyloid clearance and short-term clinical benefit has been demonstrated in the TRAILBLAZER-ALZ and other amyloid targeting therapy trials. However, the long-term link is very uncertain and the precise mechanism through which amyloid and cognitive decline are related is still unclear, and therefore there is uncertainty over (a) whether elevated amyloid levels are always a predictor of a declining cognitive trajectory and Alzheimer's disease dementia; and (b) the relative contribution of amyloid compared to other well-demonstrated predictors of cognitive decline.[89]

Therefore, we disagree with the company's assumptions summarised in Table 34 below, as we consider these to be optimistic considering the current evidence. In the EAG base case we assume that patients treated with donanemab will retain the full treatment effect for one year after stopping treatment, based on trial evidence showed in Shcherbinin et al. and CS Figure 18. This assumption should be applied to patients who are treated for a fixed period of 18 months, and to those who stop treatment after reaching amyloid clearance or due to adverse events. However, as the subgroups of patients who are treated for a fixed period of

18 months and who stop at six or 12 months due to amyloid clearance are not subsequently modelled separately, this means that all patients retain the full treatment effect until the end of cycle four and therefore patients who reach amyloid clearance at six or 12 months are assumed to retain the full treatment effect for a period of 1.5 or two years (rather than one year). This does not have any impact in the EAG base case as we are assuming no patients monitored for amyloid clearance due to limitations in PET infrastructure.

To match the company's assumption that patients take around 3.5 years to reach amyloid positivity (>24.1CL) after stopping treatment with donanemab, we assume in our base case that the treatment effect will be retained for one year and then will wane for another 2.5 years until the probability of disease progression is the same as for patients on BSC. Our clinical experts prefer this assumption rather than the company's base case which they found more speculative. We explore alternative waning periods and their impact in the model conclusions in scenario analyses in section 6.3.

Table 34 shows the company's and EAG assumptions around the treatment effect of donanemab after patient stopping treatment.

Table 34 Model assumptions around treatment effect after treatment discontinuation

Discontinuation rule	Trial period	Post-trial medium term period	Post-trial long term period
Company base case			
Fixed treatment duration of 18 months	Full treatment effect for 18 months	Full treatment effect retained for 3.5 years after stopping treatment	Treatment effect gradually wanes to zero over the following 5 years
Amyloid clearance at 6 or 12 months defined as <24.1CL at any amyloid PET scan	Full treatment effect for 6 or 12 months	Full treatment effect retained for 4 or 4.5 years after stopping treatment (dependent on patients discontinuing at 12 or 6 months, respectively)	Treatment effect gradually wanes to zero over the following 5 years
Discontinuation due to progression to the severe AD dementia health state	No treatment effect once patients progress to severe AD dementia	No treatment effect once patients progress to severe AD dementia	No treatment effect once patients progress to severe AD dementia

Discontinuation rule	Trial period	Post-trial medium term period	Post-trial long term period
Company base case			
Discontinuation due to adverse events	Full treatment effect while patients on treatment	Full treatment effect retained for 1 year after stopping treatment	Treatment effect gradually wanes to zero over the following 2.5 years
EAG base case			
Fixed treatment duration of 18 months	Same as company	Full treatment effect retained for 1 year after stopping treatment	Treatment effect gradually wanes to zero over the following 2.5 years
Amyloid clearance at 6 or 12 months defined as <24.1CL at any amyloid PET scan	Same as company	Full treatment effect retained for 1.5 or 2 years after stopping treatment (dependent on patients discontinuing at 12 or 6 months, respectively)	Treatment effect gradually wanes to zero over the following 2.5 years
Discontinuation due to progression to the severe AD dementia health state	Same as company	Same as company	Same as company
Discontinuation due to adverse events	Same as company	Same as company	Same as company

Source: Reproduced from CS Table 22 and edited to include EAG assumptions.
AD, Alzheimer disease; PET, positron emission tomography.

EAG comment on the assumptions around the long-term treatment effect of donanemab

The company's assumptions on the long-term treatment effect were based on short-term evidence, which we consider to be optimistic and so we changed these in our base case. For all patients, except those with severe Alzheimer's disease dementia, we assumed that the full treatment effect is retained for one year after stopping treatment and then gradually wanes for another 2.5 years.

4.2.9.3 Adverse events

The adverse events included in the economic model are described in CS section B.3.2.4 and outlined below.

Amyloid related imaging abnormalities (ARIA) events of all grades, applied during the first cycle of the model, as these events mostly occur in the first months after initiation of amyloid-targeting therapies.

Anaphylactic events (all grades) as well as moderate and severe injection related reactions and hypersensitivity events. Rates for these events were converted to six-month probabilities and applied for the whole trial period (i.e., three model cycles).

The incidence of adverse events for donanemab was obtained from TRAILBLAZER-ALZ 2 trial[30] and is reported in CS Table 28. No adverse events were assigned to the BSC arm of the model.

The proportion of patients discontinuing treatment with donanemab due to adverse events come from the TRAILBLAZER-ALZ 2 trial and is 13.10%.[30] Our clinical experts consider that the discontinuation rate used is reasonable. This was applied in the first cycle of the model for donanemab.

EAG comment on adverse events

We consider that the most relevant adverse events were included and correctly applied in the economic model.

4.2.10 Health related quality of life

4.2.10.1 Systematic literature review for utilities

The company conducted a systematic literature review of HRQoL studies in patients and caregivers of patients with early Alzheimer's disease. The methodology is described in CS Appendix E. The search period, coding and inclusion and exclusion criteria are discussed above in section 4.1.

The review identified 30 studies reporting utility outcomes for patients with Alzheimer's disease and their caregivers (CS Appendix E.1.7.2). Of those, three studies were conducted in the UK setting and reported EQ-5D utilities by disease severity.[90] [91] [76] [92] Table 35 presents the main characteristics and results of these three studies.

The EAG notes that the studies used to inform the utilities in the current economic model did not come from the systematic literature review conducted by the company, except one of the studies that informed the caregiver utilities.[93] Patient utilities come from the systematic literature review and meta-analysis conducted by Landeiro et al.[94] and the caregiver utilities are informed by two vignette studies conducted by Eli Lilly.[93; 95] Landeiro et al. included 12 studies conducted in the UK setting, but only four of these UK studies used the EQ-5D and reported results by disease severity (summarised in Table 35 below).[76; 96-98] We note that only two UK studies included in the systematic literature review and meta-analysis from Landeiro et al. were also included in the company's systematic literature review.[76; 99] The EAG is unclear if the remaining UK studies included in the Landeiro review were also identified by the company as we don't have access to the full list of included and excluded HRQoL studies.

Table 35 Main characteristics and results of relevant HRQoL studies conducted in the UK included in the company's and Landeiro et al. 2020 systematic literature reviews.

	Company's systematic literature review			Landeiro's systematic literature review			
	Fang et al. 2016[90]	**Froelich et al. 2021[91]**	**GERAS (2013, 2017)[a 76 92]**	**Bryan et al. 2005[96]**	**Knapp et al. 2016[97]**	**Orgeta et al. 2015[98]**	**Meta-analysis (company's base case)[94]**
Country	UK, Canada	UK, Spain, Germany	UK, France, Germany	UK	UK	UK	NA
Study design	Observational study	Observational study	Observational study	Cross-sectional study	RCT	Observational study	Systematic literature review and meta-analysis
Respondents	Patient and caregiver self-assessment	Patient and caregiver self-assessment and caregiver proxy-assessment	Caregiver proxy-assessment and self-assessment	Caregiver proxy-assessment	Caregiver proxy-assessment	Patient self-assessment and caregiver proxy-assessment	NA
Sample size	216	616	1497	64	295	478	4643 (mild) 4095 (moderate) 3864 (severe)
Health states evaluated	Mild AD and moderate AD for patients and caregivers	Mild AD and moderate AD for patients and caregivers	Mild AD, moderate AD and moderately severe/severe AD for patients and caregivers	Mild and moderate AD	Severe AD	Mild and moderate AD	NA
Instrument used to measure disease severity	Functional Assessment Staging in Alzheimer's Disease Scale	MMSE	MMSE	CDR	MMSE	CDR	NA

	Company's systematic literature review			Landeiro's systematic literature review			
	Fang et al. 2016[90]	**Froelich et al. 2021[91]**	**GERAS (2013, 2017)[a 76 92]**	**Bryan et al. 2005[96]**	**Knapp et al. 2016[97]**	**Orgeta et al. 2015[98]**	**Meta-analysis (company's base case)[94]**
Elicitation method tariff	EQ-5D-3L, UK tariff	EQ-5D-5L, tariff NR	EQ-5D, UK tariff for patient's and NR for caregiver's utilities	EQ-5D	EQ-5D	EQ-5D-5L	EQ-5D
Patient utilities							
Mild AD dementia, mean (95% CI)	0.85 (0.85-0.88)	Self-assessment: 0.85 (SD 0.17) Caregiver-proxy assessment: 0.78 (SD 0.20)	Overall: 0.71 (0.67-0.75) UK: 0.68 (0.65-0.72)	IC: 0.57 (0.50-0.64) PC: 0.72 (0.67-0.77)	NR	Self-assessment: 0.79 (0.77-0.81) Caregiver-proxy assessment: 0.63 (0.60-0.66)	Caregiver-proxy assessment: 0.74 (0.69-0.79)
Moderate AD dementia, mean (95% CI)	0.81 (0.73-0.88)	Self-assessment: 0.85 (SD 0.18) Caregiver-proxy assessment: 0.74 (SD 0.22)	Overall: 0.64 (0.62-0.66) UK: 0.65 (0.61-0.69)	IC: 0.61 (0.54-0.68) PC: 0.69 (0.63-0.75)	NR	Self-assessment: 0.72 (0.70-0.74) Caregiver-proxy assessment: 0.52 (0.50-0.54)	Caregiver-proxy assessment: 0.59 (0.47-0.71)
Severe AD dementia, mean (95% CI)	NR	NR	Overall: 0.51 (0.48-0.54) UK: 0.48 (0.43-0.53)	NR	0.55-0.59 (0.48-0.65)	NR	Caregiver-proxy assessment: 0.36 (0.18-0.53)

	Company's systematic literature review			Landeiro's systematic literature review			
	Fang et al. 2016[90]	**Froelich et al. 2021[91]**	**GERAS (2013, 2017)[a] [76] [92]**	**Bryan et al. 2005[96]**	**Knapp et al. 2016[97]**	**Orgeta et al. 2015[98]**	**Meta-analysis (company's base case)[94]**
Caregiver utilities							
Mild AD dementia, mean (95% CI)	0.81 (0.80-0.85)	0.88 (0.14)	0.86 (SD 0.18)	NR	NR	NR	NR
Moderate AD dementia, mean (95% CI)	0.80 (0.80-0.80)	0.88 (SD 0.16)	0.85 (SD 0.19)	NR	NR	NR	NR
Severe AD dementia, mean (95% CI)	NR	NR	0.82 (SD 0.23)	NR	NR	NR	NR

Source: CS Appendix E Tables 42-44; Landeiro et al. 2020 Additional information Appendix 4 and 5.[90] [91] [76] [92; 96-98]
AD, Alzheimer's disease; CI, confidence interval; HRQoL, health-related quality of life; IC, informal caregiver; NA, not applicable; NR, not reported; PC; professional caregiver; SD, standard deviation; RCT, randomised controlled trial; UK, United Kingdom.
[a] GERAS study was also included in the systematic literature review and meta-analysis from Landeiro et al. 2020.

4.2.10.2 Study-based health related quality of life

The health-related quality of life data used in the model is described in CS section B.3.3.5. Both patient and caregiver utilities were included and are further discussed in sections 4.2.10.2.1 and 4.2.10.2.2 below. As explained in CS sections B.3.3.1 and B.3.3.2, no EQ-5D data were collected as part of the TRAILBLAZER-ALZ trials. HRQoL data was captured using the Quality of Life in Alzheimer's Disease questionnaire from the TRAILBLAZER-ALZ 2 trial but no mapping to EQ-5D was conducted by the company for the following reasons: (a) the trial duration was not long enough to adequately capture data on more severe health states; and (b) only a subset of patients or their proxy/carer answered the HRQoL questionnaire which may not be reflective of the entire trial population.

4.2.10.2.1 Patient utilities

The company base case used patient's health state utility values from the Landeiro et al.[94] fixed-effects meta-analysis. Landeiro et al. reported pooled estimates of patient utility values assessed both by the patients and their caregivers using EQ-5D data and categorised by disease severity. However, these pooled estimates combine EQ-5D scores using different countries' value sets to derive a single utility value for each health state. The NICE Reference Case specifies that health state valuations should be derived from a representative sample of the UK population,[77] and it is not clear to us whether utilities based on value sets for other countries are generalisable to the UK. Therefore, we consider this a limitation of the utility inputs from Landeiro et al.

Table 35 above presents several UK studies reporting EQ-5D utilities for Alzheimer's disease stages. The GERAS study (which patient utility data are reported by Wimo et al.[76]) has the biggest sample size (n=1497) and reports utility values for the mild, moderate and severe health states. We acknowledge that the GERAS study includes patients from countries other than the UK: France (n=419), Germany (n=552) and the UK (n=526). But the value set used to calculate overall patient utilities in the GERAS study was the UK value set. For the reasons above, we will use the utility values for the GERAS overall population in the EAG base case mild, moderate and severe Alzheimer's disease dementia health states (section 6.2). We explore the use of patient utilities from the GERAS UK population in a scenario analysis.

Utility data on MCI due to Alzheimer's disease is limited in the Landeiro review. Aye et al.,[100] a study which aimed to provide health utility estimates for MCI, reported a utility value of 0.81 for patients within this health state. The company took a more conservative approach

for MCI due to Alzheimer's disease and assumed that patients in this health state experience a similar quality of life as the general population based on mean age (78.4 years) and proportion of female patients (58.5%) in the Landeiro study, for consistency with the utility values for the other health states in the company's model which were generated from the same study. The EAG agrees with the company's approach on the utility of patients with MCI due to Alzheimer's disease. All the health state utilities (MCI, mild, moderate and severe) were then adjusted to match the characteristics of the model population in terms of age, by being multiplied by an adjustment factor obtained from the general population utilities for different ages. In the EAG base case, we have used a similar approach by using the mean age (77.6 years) and proportion of females (54.8%) from the GERAS study, with adjustment to the model population characteristics.

The patient utilities assessed by caregivers were used in the company's base case for all health states, except MCI due to Alzheimer's disease. Landeiro et al. included more studies reporting proxy-rated patient utilities (by caregivers) than self-rated patient utilities in patients with later disease stage. In general, the pooled self-rated patient utilities were higher than the proxy-rated patient utilities. For patients with severe dementia, Landeiro et al. reported a pooled patient self-rated utility of 0.82 (95% CI of 0.64-1.00) based on two studies versus a pooled patient utility assessed by caregivers of 0.36 (95% CI of 0.18-0.53) based on eight studies. The self-rated patient utility for the moderate health state (0.86) was higher than the self-rated utility for the mild health state (0.85). The utilities directly assessed by patients are considerably high and, in our view, unrealistic. We agree with the company's choice of using the caregiver assessment as a proxy to patient utilities. However, proxy utility data is not ideal and needs to be interpreted with caution, particularly in patients in the earlier stages of the disease who might be able to meaningfully assess their own HRQoL. We note that changing the patient utility values for the mild health state has a minimal impact in the model results.

The company assumed that the patient utility values were similar for patients in the community and residential care settings. Table 36 shows the utility values used in the company's and EAG base case and the EAG scenario analysis considering the subgroup of patients in the GERAS study from the UK.

Table 36 Patient utilities

	Company's base case (based on Landeiro et al. 2020 [94])	EAG base case (based on GERAS study 2013 – overall population.[76])	EAG scenario (based on GERAS study 2013 – UK population.[76])
MCI due to AD	0.76	0.77[a]	0.76[b]
Mild AD dementia	0.74	0.71	0.68
Moderate AD dementia	0.59	0.64	0.65
Severe AD dementia	0.36	0.51	0.48

Source: Landeiro et al. 2020[94] and Wimo et al. 2013.[76]
AD, Alzheimer's disease; EAG, Evidence Assessment Group.
[a] Patient utility for MCI due to AD was calculated as the general population utility based on the baseline age (77.6 years) and gender distribution (54.8% female) of the GERAS overall population.
[b] Patient utility for MCI due to AD was calculated as the general population utility based on the baseline age (78.5 years) and gender distribution (54.2% female) of the GERAS UK population.

EAG comment on patient utilities

In the company's base case, patient utilities were informed by EQ-5D data derived from different country-specific value sets which raises the question of their generalisability to the UK setting. For the EAG base case, we prefer to use patient utility estimates from the GERAS study, which was conducted in the UK, France and Germany and used the UK value set to derive utilities. We agree with the company's assumption that the utility for MCI should reflect general population utility, and that utilities should be adjusted for the age and gender mix of the modelled cohort. Although not ideal, we consider the company's option of using caregiver proxy-rated utilities rather than patient self-rated utilities to be reasonable.

4.2.10.2.2 Caregiver utilities

Caregiver utilities were derived from two vignette studies conducted by the company using a time trade-off approach.[93; 95] The company argued that the EQ-5D data may not be sensitive to measure the health-related quality of life of caregivers for patients with Alzheimer's disease. Separate utilities for the community and residential care settings and for the different types of caregivers (spouse or child) were used in the model. The categories "spouse caregiver" and "child caregiver" were used as a proxy for whether the carer lives

with the patient or not, respectively. The primary vignette study informed the health state utilities for caregivers of patients with MCI due to Alzheimer's disease and mild Alzheimer's disease dementia for the community and residential care settings and moderate Alzheimer's disease dementia in the community setting. The second vignette study informed the health state utilities of caregivers of patients with moderate Alzheimer's disease dementia in the residential care setting and severe Alzheimer's disease dementia in both community and residential care settings. Interviews were conducted with 304 general population participants across UK for the primary vignette study and 100 general population participants for the second vignette study. CS Table 32 reports the caregiver utilities used in the company's base case.

The rationale behind how the utilities from the vignette studies were attributed to each of the health states according to community and residential care settings and by type of caregiver was not clear to the EAG. Moreover, the vignette studies used the time trade-off approach, and the utilities were reported by general population participants, rather than caregiver for dementia patients, which is not in line with the NICE Reference Case.[77] NICE guidance states that the EQ-5D is the preferred instrument to measure health-related quality of life in adults.[77] It also states that in cases where EQ-5D is not the most appropriate measure, evidence of the lack of content validity, construct validity and responsiveness in a particular population should be provided and derived from a synthesis of peer-reviewed literature. In the EAG's opinion, the company has not provided sufficient convincing evidence to support the use of a different method to derive utilities for use in the economic model.

Reed et al. 2017[92] reported the GERAS study EQ-5D results for the primary caregiver of patients with Alzheimer's disease living in the community setting in the UK, France and Germany (see Table 37 below). The EAG considers the GERAS study utilities to be informative for the current economic model as they meet the NICE Reference Case (used EQ-5D data and the utilities are directly reported by UK caregivers) and the study sample size is bigger than the other studies identified in the company's review (Table 35 above). However, the utilities from the GERAS study are higher than utilities for the general population of the same age and gender distribution. Therefore, in the EAG base case, we assume that caregivers of patients with MCI due to Alzheimer's disease and mild Alzheimer's disease dementia have the same quality of life as the general population based on the caregivers' baseline age (67.8 years, weighted average of child and spouse caregivers) and gender distribution (36.4% males, weighted average of child and spouse caregivers) in the economic model. For the moderate and severe health states, we adjusted the general population utilities based on the relative decrement between health states

observed in the GERAS study. Table 37 presents the caregiver utilities used in the EAG base case.

Moreover, we did not attempt to stratify the utilities of caregivers by type of caregiver and community or residential care setting. As the available evidence is not stratified in this way, several assumptions would be needed, which would add uncertainty to the results. But we note that the GERAS study included both child and spouse caregivers.

We explored the use of the caregiver utilities from the company's vignette studies in a scenario analysis. Based on the company's assumption that a child caregiver lives away from the patient, we used utilities for caregivers not living with the patients from the second vignette study for child caregivers of patients in both community and residential care settings and spouse caregivers of patients in the residential care setting. For spouses living with the patient in the community setting, we used the utilities for caregivers living with the patient from the second vignette study. We used utilities from the primary vignette study in the MCI health state. Our suggested approach is shown in Table 37 below.

Table 37 Caregiver utilities

	GERAS study (EQ-5D)	**EAG base case (GERAS adjusted)[a]**	**EAG scenario (based on the company's vignette studies)**
Spouse caregiver in the community setting			
MCI	NR	0.81	0.82
Mild	0.86	0.80	0.79
Moderate	0.85	0.79	0.65
Severe	0.82	0.76	0.49
Child and spouse caregiver in the residential care setting and child caregiver in the community setting			
MCI	NR	0.81	0.84
Mild	0.86	0.80	0.74
Moderate	0.85	0.79	0.71
Severe	0.82	0.76	0.64

Source: Reed et al. 2017;[92] Eli Lilly data on file 2023; Belger et al. 2022.[93]
EAG, Evidence Assessment Group; NR, not reported.
[a] MCI and mild health states were assumed to be similar to general population with the same age (67.8 years) and gender distribution (36.4% males) as the caregiver population in the economic model for these two health states; utility for MCI was assumed to be the general population utility for age 67 years and for mild was assumed to be for age 68 years. Moderate and severe utilities are the GERAS study utilities adjusted to be lower than the general population utilities (moderate: 0.85*0.80/0.86=0.79; severe: 0.82*0.80/0.86=0.76).

The company multiplied the caregiver utilities by the number of caregivers per patient (1.8, as previously mentioned in section 4.2.3). This means that the company applied the same quality of life for all the caregivers, which we consider to be likely to be unrealistic. We believe that the primary caregiver would be expected to have a greater impact on their quality of life than secondary caregivers. Although we acknowledge that secondary caregivers may also experience a loss in their quality of life, there is no published evidence to inform utility estimates for the secondary caregivers. The GERAS study report utilities for the primary caregiver only. Moreover, it is not clear what number of caregivers per patient was assumed in previous NICE appraisals for Alzheimer's disease.[101] Therefore, only one caregiver per patient is modelled in the EAG base case, as in a previous cost-effectiveness study of donanemab (Table 26).[70] The EAG clinical experts believe this is a reasonable assumption. We explore a scenario where we change the number of caregivers from one to 1.8 in the EAG base case and that does not affect the model results to a great extent (section 6.3).

EAG comment on caregiver utilities

The EAG considers that the company has provided insufficient evidence to justify the conclusion that the EQ-5D is an inappropriate measure of health-related quality of life for caregivers of patients with Alzheimer's disease. EQ-5D data directly reported by caregivers is therefore a more appropriate source and is aligned with the NICE Reference Case.[77] For the EAG base case, we use general population utilities adjusted to reflect caregiver utilities reported in the GERAS study. We model one caregiver per patient in the EAG base case.

4.2.10.3 Adverse event utility decrements

The adverse event utility decrements were applied in the company's model and are described in CS section B.3.3.4.

For symptomatic ARIA events, the disutility value for headache (-0.14) was used as a proxy, as headache was the most reported symptom among patients with ARIA. This was applied in the model as a one-time utility decrement for the average duration of ARIA events (72.4 days). The disutility of headache in the UK was obtained from Xu et al.[102]

For anaphylactic reaction, the company applied a 15% reduction in patients' baseline utility for a duration of 30 days based on Hannouf et al.,[103] resulting in a utility decrement of -0.112 (formula corrected in response to clarification question B20). We consider that the value reported by the company in the text response to clarification question B20 (-0.012) is incorrect, as it is different from the value reported in the updated company's model (-0.112).

For injection related reactions and hypersensitivity, no utility decrement was applied in the model. The company assumed that patients are effectively treated for these adverse events and the impact on quality of life is minimal.

EAG comment on adverse event utility decrements

The EAG considers that the utility decrements were correctly applied in the company's model although we are unclear whether the disutility of headache is underestimating the loss in quality of life experienced by patients with ARIA events. We note that applying a greater disutility for ARIA events is not likely to have a measurable impact in the model results. However, this might change if long-term follow up shows that ARIA events have a longer-term impact in patients' lives.

4.2.11 Resources and costs

The following costs and resource use were included in the company analysis: drug acquisition, administration and background therapy costs (CS B.3.4.1), diagnostic and monitoring costs (CS B.3.4.2), health care costs, including residential care costs (CS B.3.4.3) and adverse event costs (CS B.3.4.4). Where necessary, costs were inflated using the Consumer Price Index including owner occupiers' housing costs (CPIH).[71]

4.2.11.1 Literature review of cost and resource studies

The company conducted a systematic literature review relating to costs and resource use, including indirect costs (section 4.1). Eligibility criteria are shown in CS Appendix E Table 11. Results are shown in CS Appendix E sections E.1.6.3, E.1.6.4, E.1.7.3 and E.1.7.4. The CS does not comment on which study is the most relevant or whether any studies informed the company model.

4.2.11.2 Drug acquisition and administration costs

CS section B.3.4.1 presents the drug acquisition and administration costs. The dosing information for donanemab is shown in Table 38 (CS Tables 33 and 34). Donanemab is administered by intravenous infusion every four weeks for up to 18 months. The recommended dosage consists of a loading dose of 700mg for the first three months and then a maintenance dose of 1400mg thereafter. Donanemab is offered to the NHS with a Patient Access Scheme (PAS) confidential price discount. The cost of a 350mg vial is [redacted]

Donanemab is administered over at least 30 minutes, and patients should be observed post-infusion for 30 minutes. The administration costs used in the model is £207.59 (SB12Z (Deliver simple parenteral chemotherapy at first attendance, NHS reference Costs

2021/22[104]). A relative dose intensity of 95.1% was applied in the model, based on a proportion of patients who interrupted treatment due to ARIA events as observed in the TRAILBLAZER-ALZ 2 trial.

Table 38 Donanemab drug acquisition costs with PAS price applied.

Treatment	Pack/vial cost	Pack/vial size	Strength	mg per pack/vial	Cost per mg (PAS)
Donanemab	[redacted]	20.0 ml	17.5 mg/ml	350.00 mg	[redacted]

Source: CS Table 33.
PAS, Patient Access Scheme

In the company's base case, patients are treated for 18 months with donanemab unless they discontinue treatment due to confirmed amyloid clearance at six or 12 months, adverse events or progression to severe Alzheimer's disease dementia.

Clinical advice to the EAG was that patients would require additional outpatient consultation visits at the start of treatment, during titration of the treatment dose, and then every 3-6 months. If the patient had an adverse event, there might be an additional clinic visit or if an existing scheduled visit was booked, this might be brought forward.

4.2.11.3 Background therapy costs

The costs of concomitant medication (including memantine and acetylcholinesterase inhibitors) are shown in CS Table 36. The unit costs are taken from the British National Formulary.[105] The proportion of patients on each treatment are estimated by the company, based on an Adelphi survey. We note that the proportion of patients receiving acetylcholinesterase inhibitors per health state is not the same in CS section B.1.3.4 and CS Table 36. For instance, in CS section B.1.3.4, it is stated that [redacted] of patients with MCI due to Alzheimer's disease and [redacted] of patients with mild Alzheimer's disease dementia receive acetylcholinesterase inhibitors. In CS Table 36 as well as in the company's model, the proportions having acetylcholinesterase inhibitors are [redacted] and [redacted] for MCI and mild patients, respectively. The reason for this discrepancy is not clear to the EAG, but we note that using the values reported in CS section B.1.3.4 have a negligible impact in the model results.

4.2.11.4 Diagnostic and monitoring resource use and costs

Diagnostic and monitoring costs are discussed in CS section B.3.4.2.

4.2.11.4.1 Diagnostic resource use

In order to be eligible for treatment with donanemab, patients are required to be beta-amyloid positive. The model includes the cost of testing for amyloid positivity as this is not currently a routine part of clinical practice in the UK. In addition to amyloid testing, patients are also tested for APOE ε4 status. The resources required for the diagnostic testing are shown in Table 39 (CS Table 38). In the base case, it was assumed that a factor of two is applied to the proportions of patients receiving cerebrospinal fluid analysis (CSF) and amyloid positron emission tomography (PET) scans to account for patients who receive a diagnostic test but do not go on to receive treatment with donanemab. In response to clarification question B26a, the company explained that this assumption was based on clinical expert advice to the company and on a large study (n=19,000) conducted by Jansen et al., showing that 51% of MCI patients and 79-87% of mild patients had amyloid positivity.[106] Also, expert opinion provided to the EAG considered that it is reasonable to assume that approximately half of the people screened will be amyloid positive. We consider therefore that assuming two screening tests per person is a reasonable assumption. The company assumes that 75% of patients have an MRI, as 25% of people would have already had an MRI in the past year. In response to clarification B29, the company stated that this is based on clinical advice and conducted a scenario analysis showing that assuming that 100% of patients need to have an MRI at baseline has a minimal impact in the model results (Table 24 of clarification response document). Clinical advice to the EAG suggests that the use of diagnostic testing showed in Table 39 is reasonable.

The company conducted scenario analyses around (a) the number of screening tests to identify one eligible patient to receive treatment with donanemab, and (b) assuming that a hypothetical blood-based biomarker was available to identify and treat amyloid positivity (CS Table 51). None of the scenarios change the ICER to a great extent. The EAG consider that patients would also require a consultant outpatient appointment as part of the diagnostic process and we added a cost of £221.91 (NHS reference costs 21/22: Service code 400: Consultant-Led Neurology Outpatient Visit[104]) for this to the cost of the APOE ε4 diagnostic test (£43.81, see Table 40 below) to our base case in section 6.2.

Table 39 Diagnostic testing descriptions and resource use

Test	Description	Base case resource use per patient
CSF	Amyloid detection	90%[a]
Amyloid PET scan	Amyloid detection	10%[a]

MRI scan	MRI conducted before treatment to check patient meets eligibility criteria	75%
APoE ε4 test	Genetic test to identify carriers of the APOE ε4 gene	100%
Blood-based biomarker test	Potential use as screening test	Only included in scenario analysis

Source: Reproduced from CS Table 38.
APOE, apolipoprotein E; ARIA, amyloid-related imaging abnormalities; CSF, cerebrospinal fluid; MRI, magnetic resonance imaging; PET, positron emission tomography.
[a] A factor of 2 is applied to these proportions to account for patients who receive a diagnostic test but do not go on to receive treatment with donanemab.

4.2.11.4.2 Monitoring resource use

In the base case, the company assumed that 10% of patients receiving donanemab would be able to be monitored using PET scans for amyloid positivity and then a proportion of these patients would stop treatment before 18 months, either at six or 12 months (see section 4.2.4 above). Patients need to be monitored during the treatment period for ARIA events, using MRI scans. It was assumed that patients would receive three regular MRI scans during the treatment period: prior to the second dose, prior to dose increase and prior to the seventh dose.

The EAG notes that patients do not receive outpatient consultant visits in the model. In response to clarification question B25, the company stated that the NHS reference costs cover the costs of outpatient consultant visits. The EAG disagrees and considers that these need to be separately costed. We have therefore included in the EAG base case analysis the cost of one outpatient consultant visit per cycle during the treatment period (i.e., a total of 3 consultations over 18 months), with which our clinical experts agreed. In response to clarification question B25, the company included the option to include outpatient consultant visits, with a cost of £211.91 per consultant-led consultation from the NHS reference costs.

4.2.11.4.3 Diagnostic and monitoring costs

The unit costs of the diagnostic and monitoring tests are shown in CS Table 37 and Table 40 below. The weighted average cost for diagnostic testing was applied in the first cycle of the model.

As explained above, we consider that patients would require an outpatient appointment for the diagnostic process and added this cost (£221.91) to the cost of APOE ε4 diagnostic test in our base case. Clinical experts to the EAG are of the opinion that most carriers of an APOE ε4 allele (homozygotes and heterozygotes) would need some counselling as genetic

results are difficult to understand and they should be always explained to the patients even if they are not eligible for treatment. One of our experts said that counselling could be part of a normal outpatient appointment already planned as part of the diagnostic process and not always as a separate appointment. The EAG did not include a counselling appointment in their base case but explore this as part of the NHSE model scenario in section 6.3.1.

Table 40 Unit costs for diagnostic and monitoring resources

Imaging/testing	Company's base case (unit costs)	Source
MRI scan	£197.34	NHS Costs – Year 2021/22; Currency code – RD01A
Amyloid PET scan	[redacted]	-
Amyloid PET procedure only	£607.85	NHS Costs – Year 2021/22; Currency code – RN01A
Tracer	[redacted]	Assumption based on a draft price for an amyloid radiotracer in the UK
Blood-based biomarkers[a]	£43.81	NHS Costs – Year 2021/22; Currency code – DAPS02
CSF	£406.00	NHS Costs – Year 2021/22; Currency code – HC72A
APOE ε4 test	£43.81	NHS Costs – Year 2021/22; Currency code – DAPS02

Source: Reproduced from CS Table 37.
APOE, apolipoprotein E; CSF, cerebrospinal fluid; MRI, magnetic resonance imaging; PET, positron emission tomography.
[a] Blood-based biomarkers are not yet available in the UK as such, this cost is an assumption based on the currency code for 'direct access pathology services: histopathology and histology'.

We conduct a scenario analysis in section 6.3.1 using the costs and resources from the NHSE model.

4.2.11.5 Health care costs

CS section B.3.4.3 reports the health state costs and resource use. The health state unit costs were taken from the PSSRU[71] report for mild, moderate and severe Alzheimer's disease and for residential care. Unit costs for MCI due to Alzheimer's disease were taken from the study by Wittenberg et al.[107] and inflated to 2022 prices, as the PSSRU report does not report these costs. The health state unit costs are shown in CS Table 39. The company conducted a scenario analysis using the costing from Wittenberg et al. (CS Table 40) and including informal care costs (CS Table 41).

The EAG notes that costs from the PSSRU report were also derived from the study by Wittenberg et al., however they include unpaid care costs. Therefore, we prefer to use the values in CS Table 40 in the EAG base case, which show the health care costs from Wittenberg et al. but do not include unpaid care costs. The EAG noted that the MCI due to Alzheimer's disease health state costs are different in CS Tables 39 and 40, although both values are taken from the same source. The company confirmed that the value in CS Table 40 is incorrect in response to clarification question B24 and we should consider the health state cost in CS Table 39.

In addition, the model included a one-off terminal care cost of £7,274 from Jones et al.[71] We note that the healthcare estimates from Wittenberg et al. include terminal care costs, so, to avoid double counting, we prefer to omit this additional cost from the analysis.

4.2.11.6 Adverse event costs

The unit costs for treating adverse events are shown in CS Table 42 (CS section B.3.4.4). The frequency of adverse events is shown in CS Table 28. The unit costs associated with each adverse event are multiplied by the proportion of patients experiencing each adverse event. The costs of ARIA events were applied in the first cycle of the model while for the other adverse events, the costs were applied for the duration of the trial period (3 cycles). The cost of treating ARIA events was assumed to be £410.62 per symptomatic patient. The cost included two MRIs and 1.8% of patients requiring an emergency department visit. One of our experts agreed with the resources included in the company's model to treat symptomatic ARIA events, but the other expert considered that two telephone consultations should also be included to triage the adverse event and agree on a plan for MRIs. We note that adding these telephone consultations to the model has a minimal impact in the model results.

Although we consider that adverse events should have one consultation visit associated with them, additional consultation visits may not be necessary above those added for monitoring costs in section 4.2.11.4.

EAG comment on resources and costs

The company's estimates for the diagnostic and monitoring of patients with early Alzheimer's disease are broadly reasonable and were agreed by our clinical experts, with exception for the costing of APOE test. For these we expect patients to receive an outpatient appointment and, sometimes, a further genetic counselling appointment. We think that assuming two screening tests to identify one eligible patient to be treated with donanemab is plausible. We consider that

the number of outpatient consultations has been underestimated so we added these to our base case analysis. The EAG prefers to use the health care costs from Wittenberg et al. that do not include unpaid care costs. To avoid double counting, terminal care costs are not included in the EAG base case.

5 COST EFFECTIVENESS RESULTS

5.1 Company's cost effectiveness results

In response to the clarification question B20, the company updated their calculation of the disutility values associated with anaphylactic reaction. The company cost-effectiveness results for donanemab versus BSC with this update are shown in Table 41 using the PAS discount for donanemab. The company's change only has a minor impact on the model results. As stated in section 7 below, the company acknowledge that donanemab does not meet the criteria for a severity modifier in response to clarification question B33. We present the company results with the severity modifier in section 6.1 and without the severity modifier below. The ICER is £19,736 per QALY with a QALY gain of 0.71 and an additional cost of £13,953.

Table 41 Company revised base case results with PAS for donanemab

Treatment	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER versus baseline (£/QALY)
Donanemab	[redacted]	1.76	£13,953	0.71	£19,736
BSC	[redacted]	1.05	-	-	-

Source: Partly reproduced from Table 27 of clarification response document and company's revised model ('Deterministic results' sheet).
BSC, best supportive care; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year

5.1.1 Deterministic sensitivity analyses

The company considers 109 parameters in their one-way sensitivity analyses (OWSA), according to the company model (DSA inputs sheet). Variations in input parameters are based on 95% confidence intervals, calculated using the standard error. If the standard error was not reported, the company uses a variation of +/-20% of the mean base case value.

The results for the one-way sensitivity analyses (OWSA) are shown in CS Figure 23. The results show that the variables that have the largest impact on the results were the treatment effect of donanemab versus BSC in patients with mild Alzheimer's disease dementia, the direct health and social care costs in severe Alzheimer's disease dementia and the relative dose intensity applied to donanemab.

5.1.2 Probabilistic sensitivity analysis

The company conducted a probabilistic sensitivity analysis using 2000 simulations. The same parameters included in the OWSA were also included in the PSA. The EAG considered that the distributions used in the PSA were appropriate.

The probabilistic results are shown in CS Table 50. The EAG notes that probabilistic results are similar to the deterministic results. The results are shown as a scatterplot of donanemab against BSC in CS Figure 21. In addition, a cost effectiveness acceptability curve (CEAC) is shown in CS Figure 22. The PSA estimated the probability of donanemab being cost effective at 63% and 87% at willingness-to-pay thresholds of £20,000 and £30,000 per QALY, respectively.

5.1.3 Scenario analysis

The company conducted 18 probabilistic scenario analyses using 2000 iterations for each scenario and the results for these are reported in CS Table 51. A description of the scenario analyses is given in CS section B.3.10.3. We replicated the company's scenario analyses without the severity multiplier, and these are presented deterministically in Table 42 below. The results of the scenario analyses vary between £7,783 (scenario 2: All patients start in the MCI due to Alzheimer's disease health state) to £31,379 per QALY (scenario 17: health state costs from Wittenberg et al.).

The EAG was unable to replicate the results for scenarios 5 and 8, and the company confirmed in clarification questions B31 and B32 that the results were incorrect in CS Table 51. The company has shown the correct results in the company clarification response document Tables 25 and 26. The EAG is still unable to replicate the results for scenario 8 (blood-based biomarker test becomes available (rule in)) with the instructions given by the company in their response to clarification question B32.

Table 42 EAG replication of company scenarios (deterministic, no severity multiplier)

Scenario	Description	Incremental Costs (£)	Incremental QALYs	ICER (£/QALY)
Base Case		£13,953	0.71	£19,736
1	Discount rate of 1.5%	£12,400	0.78	£15,855
2	100% patients enter model in MCI due to AD	£6,953	0.89	£7,783
3	100% patients enter model in mild dementia due to AD	£15,744	0.66	£23,878
4	Fixed duration of treatment only	£14,345	0.71	£20,291

Scenario	Description	Incremental Costs (£)	Incremental QALYs	ICER (£/QALY)
5	Treat-to-clear only	£10,045	0.71	£14,209
6	4 diagnostic tests required to identify one eligible patient	£15,047	0.71	£21,283
7	Blood-based biomarker test becomes available (rule-out)	£13,450	0.71	£19,024
8	Blood-based biomarker test becomes available (rule-in)	£12,903	0.71	£18,251
9	Transition probabilities (Potashman et al.)	£13,385	0.70	£19,069
10	Caregiver utility values (unadjusted)	£13,953	0.62	£22,654
11	Treatment effect waning (medium-term) based on amyloid positivity level of 30cL	£13,222	0.73	£18,068
12	Patients who discontinue due to AE wane treatment over 10 cycles	£13,378	0.73	£18,389
13	Patients who discontinue due to AE wane treatment over 1 cycle	£14,571	0.68	£21,302
14	Treatment waning effect applied over 5 cycles (patients who did not discontinue due to AE)	£15,337	0.66	£23,239
15	Treatment waning effect applied over 15 cycles (patients who did not discontinue due to AE)	£13,076	0.74	£17,748
16	Mortality based on meta-analysis	£16,677	0.63	£26,329
17	Direct Health and Social Care Costs (Wittenberg et al.)	£22,185	0.71	£31,379
18	Informal care costs included (Wittenberg et al.)	£21,077	0.71	£29,812

5.2 Model validation and face validity check

5.2.1 Company validation

The company's approach to validating their model is described in CS Section B.3.13.1. The CS states that the following steps were taken: extreme-value testing (setting inputs to extremely high and low values and checking for feasibility), technical review (model programming was reviewed by a senior modeller who was not part of the project team, including checking links and mathematical formulas), and input verification (checking parameters against source documents).

Following the validation process, errors identified by the validator were corrected, and the revised model was rechecked by the validator.

In response to clarification question B35, the company compared the proportion of patients in each of the health states over the trial duration with those in the TRAILBLAZER-ALZ 2 trial data. The results are shown in clarification response document Figures 7-10. Generally, the alignment between the model and trial data are better in the MCI and mild AD health states and less good for the moderate and severe health states. The company states that the discrepancies are due to differences between the trial and NACC population. Further, the NACC population progresses slightly faster than the trial population, the model assigns relatively more patients to the moderate and severe health states over the first 18 months than is seen in the trial, and relatively fewer patients to the mild health state. The company consider that the NACC data set is more reflective of a real-world context than the patients enrolled in the clinical trial.

5.2.2 EAG validation

The EAG conducted a range of tests to verify model inputs, calculations and outputs:

- Cross-checking all parameter inputs against values reported in the CS and cited sources.
- Checking all model outputs against results cited in the CS, including the base case, deterministic sensitivity analyses, scenario analyses and probabilistic sensitivity analyses.
- Manually running scenarios and checking model outputs against results reported in the CS for the deterministic sensitivity analyses and scenario analyses.
- Checking the individual equations within the model ('white box' checks), including replicating parts of the model.

- Applying a range of extreme value and logic tests to check the plausibility of changes in results when parameters are changed ('black box' checks).

The EAG did not discover any technical errors in the model.

5.2.3 EAG summary of key issues and additional analyses

A full summary of EAG observations on key aspects of the company's economic model is presented in Table 43.

Table 43 EAG observations of the key aspects of the company's economic model

Parameter	Company base case	EAG comment	EAG base case
Model structure			
Model structure	Markov model with five health states	We agree	No change
Population	Section 4.2.3	We agree	No change
Number of caregivers per patient	1.8	We consider that the primary caregiver has a more significant and measurable impact on quality of life than secondary caregivers. Assuming different utilities for the primary or secondary caregivers will add uncertainty to the model as there is no utility data for the secondary caregivers.	1
Treatment duration of donanemab	90% of patients treated for a fixed period of 18 months and 10% treated until reaching amyloid clearance (<24.1CL)	According to the company and our experts, there is limited infrastructure availability in the UK, and it is unlikely that patients will be monitored for amyloid clearance in the current circumstances.	100% of patients treated for a fixed period of 18 months
Comparators	BSC without donanemab	We agree	No change
Perspective	NHS and PSS	We agree	No change
Time horizon	Lifetime	We agree	No change
Discounting	3.5% for costs and outcomes	We agree	No change

Parameter	Company base case	EAG comment	EAG base case
Natural history disease			
Transition probabilities	Probabilities obtained from the US NACC dataset	We consider the use of the US NACC dataset acceptable in the absence of relevant UK data. However, we note that data from the incident cohort of the NACC company's study is not available to the EAG so that we can test the impact in the model results.	No change We test using the transition probabilities from the prevalent cohort of the Potashman study excluding and including the probability of improvement in scenario analyses.
Risk of residential care	Obtained from the Spackman et al. 2012 study	The GERAS study is more recent than the Spackman study and includes patients from the UK	Annual probabilities of residential care from the GERAS study. We test using the Lin et al. 2022 probabilities in scenario analysis.
Mortality			
AD-related mortality	HR of 2.55 for all health states, except MCI due to AD	According to previous cost-effectiveness studies of donanemab, we consider that it is more plausible that the mortality HR increases according to disease severity rather than being constant.	Mortality HRs from Crowell et al. (age 80 years). We test using the Ross et al. and the Lin et al. mortality hazard ratios in scenario analyses.
Treatment-specific mortality	Additional mortality risk of 0.35% applied once in the model	We agree	No change
Treatment effectiveness			
Treatment effect of donanemab within the trial period	HR for disease progression of 0.62 based on CDR-SB outcomes from the TRAILBLAZER-ALZ 2 trial	A pooled HR for disease progression (CDR-SB) based on meta-analysis of both TRAILBLAZER studies would be useful to test in the model as a scenario or potentially to be used in the EAG base case.	No change We test using iADRS in scenario analysis.
Long-term treatment effect for patients	Full treatment effect retained for 3.5 years after stopping	In the absence of long-term data on the treatment effect of	Full treatment effect retained for 1 year after stopping

Parameter	Company base case	EAG comment	EAG base case
treated for a fixed period of 18 months	treatment and then waning to zero for the following 5 years	donanemab, we consider the company's assumptions to be very optimistic. Our experts also agree that this is an area of great uncertainty.	treatment and then waning to zero for the following 2.5 years. We test using alternative assumptions in scenario analyses: a) waning period of 1 year b) waning period of 3 years c) full treatment effect retained for 3.5 years and waning period of 5 years (company's base case) d) waning period of 7.5 years (company's scenario)
Long-term treatment effect for patients who achieved amyloid clearance at 6 or 12 months	Full treatment effect retained for 4.5 or 4 years after stopping treatment and then waning for the following 5 years	See comment above for patients treated for a fixed period of 18 months	Full treatment effect retained for 2 or 1.5 years after stopping treatment and then waning for the following 2.5 years. We test using alternative assumptions in scenario analyses: a) waning period of 1 year b) waning period of 3 years c) full treatment effect retained for 3.5 years and waning period of 5 years (company's base case) d) waning period of 7.5 years (company's scenario)
Long-term treatment effect for patients who discontinue treatment due to AEs	Full treatment effect retained for 1 year after stopping treatment and then waning for the following 2.5 years	We agree	No change. We test using alternative waning periods in scenario analyses: a) 6 months (company's scenario)

Parameter	Company base case	EAG comment	EAG base case
			b) 1 year c) 5 years (company's scenario)
Long-term treatment effect for patients who progress to severe AD dementia	No treatment effect once patients enter the severe AD dementia health state	We agree	No change
Adverse events	Section 4.2.9.3	We agree	No change
Utilities			
Patient utilities	Utilities for mild, moderate and severe AD dementia health states from Landeiro et al. 2020	The Landeiro study combines EQ-5D scores which used different value sets (including the UK value set and others) to derive utilities. This is not aligned with the NICE guidance.	Utilities for mild, moderate and severe AD dementia health states from the overall population of GERAS study. We test using the GERAS UK population utilities in a scenario analysis.
Caregiver utilities	Utilities from two vignette studies based on TTO approach	Use EQ-5D to derive utilities, as recommended in the NICE guidance.	Utilities for MCI due to AD and mild AD dementia similar to the general population; utilities for moderate and severe AD dementia from the GERAS study and adjusted for the general population utilities. We test using the caregiver utilities from the company's vignette studies, as shown in Table 34, in scenario analysis.
AEs disutilities	Section 4.2.9.3	We agree	No change
Severity modifier	At their clarification response, the company assumed a severity modifier of 1.0.	We agree	No change
Resource use and costs			
Drug acquisition and administration	Section 4.2.11.2	We agree	No change We test using the NHSE model costs in a scenario analysis.

Parameter	Company base case	EAG comment	EAG base case
Diagnostic and monitoring costs	Section 4.2.11.4	Patients would require additional outpatient consultant appointments	One additional consultation appointment added as part of the diagnostic process. Plus, one additional consultation appointment added for each treatment cycle during trial period (i.e., a total of 3 consultations over 18 months), as part of monitoring. We test using the NHSE model costs in a scenario analysis.
Healthcare resource use	The health state costs were from the study by Wittenberg et al, however they include unpaid care costs.	We prefer to use these costs without unpaid care costs. We note that these costs include terminal care costs. Patients would require additional outpatient consultant appointments	We use the values in CS Table 40 in the EAG base case which show the health care costs from Wittenberg et al. but do not include unpaid care costs. We do not apply terminal care costs to avoid double counting.
Adverse event costs	Section 4.2.11.6	We agree	No change

AD, Alzheimer's disease; AE, adverse events; BSC, best supportive care; CDR-SB, Clinical Dementia Rating Sum of Boxes; CS, company submission; EAG, External Assessment Group; HR, hazard ratio; iADRS, integrated Alzheimer's Disease Rating Scale; MCI, mild cognitive impairment; NHS, National Health Service; NICE, The National Institute for Health and Care Excellence; PSS, Personal Social Services; TTO, time trade-off; UK, United Kingdom; US NACC, United States National Alzheimer's Coordinating Centre.

6 EAG'S ADDITIONAL ANALYSES

6.1 Exploratory and sensitivity analyses undertaken by the EAG

The company acknowledged in their clarification response that donanemab did not meet the eligibility for a severity modifier. We show the results in Table 44 with their previous assumption of a severity modifier of 1.2. The ICER is £16,447 per QALY, with a QALY gain of 0.85 and an additional cost of £13,953.

Table 44 Company revised base case results

Treatment	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER versus baseline (£/QALY)
Donanemab	[redacted]	2.11	£13,953	0.85	£16,447
BSC	[redacted]	1.26	-	-	-

Source: Company's revised model ('Deterministic results' sheet).
BSC, best supportive care; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year

6.2 EAG's preferred assumptions

Based on the EAG critique of the company's model discussed in Table 43, we have identified several key aspects of the company base case with which we disagree. Our preferred model assumptions are the following:

1. **Treatment duration of donanemab**: No patients discontinue before 18 months due to reaching amyloid clearance.
2. **Risk of residential care**: Annual probabilities of moving to residential care from the GERAS study[84] (see Table 32).
3. **Mortality risk for Alzheimer's disease**: Hazard ratios are assumed to increase with progression of disease and were taken from Crowell et al[1] (see Table 33). **(Key issue)**
4. **Long-term treatment effect**: Full treatment effect retained for one year after stopping treatment and then waned for the following 2.5 years. **(Key issue)**
5. **Patient utility:** Use utility values from GERAS study,[76] rather than Landeiro et al.[94] (see Table 36). **(Key issue)**
6. **Caregiver disutility**: Caregiver utilities taken from the GERAS study,[92] rather than the company's vignettes[93; 95] (see Table 37). **(Key issue)**
7. Number of caregivers per patient: Reduced from 1.8 to 1.

8. **Health care resource use:** Use health state costs from Wittenberg et al.,[107] which does not include unpaid care costs. We do not apply terminal care costs to avoid double counting (as these are included in the Wittenberg et al. estimates).
9. **Outpatient consultations:** We include an outpatient consultation for the diagnostic process and one consultation per model cycle for the first 18 months.

Table 45 shows the cumulative cost-effectiveness results of applying the EAG preferred model assumptions to the company's base case including the PAS discount for donanemab. Incorporating all the EAG assumptions, the ICER for donanemab vs BSC increases to £149,531 per QALY.

The change that has the most significant impact on the cost-effectiveness results is changing the assumptions for how long the treatment effect lasts, using an alternative source for the caregiver disutilities and alternative mortality hazard ratios.

Table 45 EAG's preferred model assumptions: cumulative impact (deterministic)

Preferred assumption	Treatment	Total costs	Total QALYs	Cumulative ICER £/QALY
Company base-case	Donanemab	[redacted]	1.76	£19,736
	BSC	[redacted]	1.05	
+ No patients discontinue due to reaching amyloid clearance before 18 months	Donanemab	[redacted]	1.76	£20,291
	BSC	[redacted]	1.05	
+ Full treatment effect for 1 year after stopping treatment, then waned for the following 2.5 years	Donanemab	[redacted]	1.52	£46,113
	BSC	[redacted]	1.05	
+ Annual probabilities of moving to residential care from the GERAS study	Donanemab	[redacted]	1.81	£51,314
	BSC	[redacted]	1.37	
+ Mortality hazard ratios taken from Crowell 2023	Donanemab	[redacted]	1.95	£73,558
	BSC	[redacted]	1.53	
+ Patient utility from GERAS study	Donanemab	[redacted]	2.20	£86,350
	BSC	[redacted]	1.84	
+ Caregiver disutility: GERAS study	Donanemab	[redacted]	3.77	£134,039
	BSC	[redacted]	3.54	
+ One caregiver per patient	Donanemab	[redacted]	3.89	£137,775

Preferred assumption	Treatment	Total costs	Total QALYs	Cumulative ICER £/QALY
	BSC	[redacted]	3.67	
+ Health care resource use does not include unpaid care costs	Donanemab	[redacted]	3.89	£145,894
	BSC	[redacted]	3.67	
+ Double counting of terminal care costs removed	Donanemab	[redacted]	3.89	£146,133
	BSC	[redacted]	3.67	
+ One outpatient consultation for diagnosis process and per model cycle up to 18 months	Donanemab	[redacted]	3.89	£149,531
	BSC	[redacted]	3.67	
EAG base case	Donanemab	[redacted]	3.89	£149,531
	BSC	[redacted]	3.67	

Source: Produced by the EAG from an adapted version of the company's revised model.
BSC, best supportive care; ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life-years

6.3 EAG scenario analyses

We performed a range of scenario analyses with the EAG base case to analyse the impact of changing some model assumptions on the final cost-effectiveness results. Table 46 below summarises the results of the scenario analyses on the EAG base case. The following scenarios were conducted:

- Selection of the company's scenario analyses (CS Table 51)
- Number of caregivers per patient: we test using 1.8 caregivers per patients as in the company's base case.
- Treatment duration of donanemab: we test assuming that 10% of patients discontinue before 18 months due to reaching amyloid clearance as in the company's base case.
- Transition probabilities: we test using transition probabilities from the prevalent cohort of the Potashman study,[79] both excluding and including improvement from more severe to milder health states of the disease (see Table 31).
- Risk of residential care: we test using the probabilities of moving to residential care from Lin et al.[70] (see Table 32).
- Mortality risk for Alzheimer's disease: we test using the mortality hazard ratios from Ross et al.[69] and Lin et al.[70] and the company's original estimates (see Table 33).
- Treatment effect of donanemab: we test using a hazard ratio for disease progression based on iADRS outcomes from the TRAILBLAZER-ALZ 2 trial (HR = 0.7) (see section 3.2.5.3 above).

- Long-term treatment effect: we test using alternative assumptions for the duration of full treatment effect and waning periods (see Table 43).
- Patient utilities: we test using the patient utilities from the Landeiro et al.[94] study and the UK population of the GERAS study[76] (see Table 36).
- Caregiver utilities: we test using the caregiver utilities from the company's vignette studies[93; 95] from the company's base case and after the EAG adjustment as shown in Table 37.
- The scenarios that had the largest impact on the model results were changing the mortality hazard ratios, the assumptions around the duration of the treatment effect and using the treatment effect based on iADRS.
- Using the mortality hazard ratios from the Office of National Statistics (company's original assumption) increases the ICER to £213,392 per QALY. Using alternative assumptions around the duration of treatment effect the ICER varies between £94,223 and £184,546 per QALY. Using the treatment effect based on the iADRS increases the ICER to £196,951 per QALY.

Table 46 EAG scenario analyses using the EAG's base case (deterministic)

Scenario	EAG's preferred assumption	Scenario value	ICER £/QALY
EAG base case			£149,531
Company scenario analyses			
Discount rate	3.5%	1.5%	£135,280
Initial patient population	20.4% MCI due to AD, 79.6% mild AD	100% MCI due to AD	£101,990
		100% mild AD	£166,905
Patients screened for amyloid clearance	0%	100%	£129,959
Diagnostic tests required per eligible patient identified	2	4	£154,381
Transition probabilities	NACC analysis (prevalent cohort, no improvement)	Potashman scenario (incident cohort, no improvement)	£143,492
Waning duration after discontinuation due to AE	5 cycles	10 cycles	£142,466
		1 cycle	£158,172

Scenario	EAG's preferred assumption	Scenario value	ICER £/QALY
Waning duration for patients discontinuing after fixed duration of 18 months or amyloid clearance.	5 cycles	15 cycles	£108,566
EAG scenario analyses			
Patients discontinue before 18 months due to reaching amyloid clearance	0% patients discontinue before 18 months	10% patients discontinue before 18 months	£147,742
Transition probabilities	Company's analysis of NACC data (prevalent cohort, no improvement)	Potashman (prevalent cohort, no improvement)	£143,059
		Potashman (prevalent cohort with improvement)	£135,885
Risk of residential care	GERAS study	Lin et al. 2022	£145,686
Mortality hazard ratios	Crowell et al 2023	Ross et al. 2022	£162,803
		Lin et al. 2022	£153,570
		ONS, 2023	£213,392
Treatment effect of donanemab	Based on CDR-SB	Based on iADRS	£196,951
Long term treatment effect for patients discontinuing due to AEs	Full treatment effect retained for 1 year, then waning to zero over the following 2.5 years	Waning period of 1 year	£155,702
Long term treatment effect for patients discontinuing after fixed duration of 18 months or amyloid clearance	Full treatment effect retained for 1 year after stopping treatment (2.5 years from baseline), then waning to zero over the following 2.5 years	Full effect for 2.5 years, waning period of 1 year	£184,546
		Full treatment effect for 2.5 years, waning period of 3 years	£141,905
		Full treatment effect of 5 years, waning	£94,223

Scenario	EAG's preferred assumption	Scenario value	ICER £/QALY
		period 5 years (company's base case)	
Patient utilities	GERAS study (overall)	Landeiro study	£117,053
		GERAS study UK	£151,278
Caregiver disutilities	GERAS study	Company's vignette studies (original)	£113,680
	GERAS study	Company's vignette (EAG adjustment)	£120,530
Mean number of caregivers per patient	1 caregiver per patient	1.8 caregivers per patient	£145,476

BSC, best supportive care; ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life-years; NHSE, National Health Service in England;

6.3.1 NHSE costing scenario

NICE requested that we conducted a scenario using the NHSE model for Alzheimer's disease diagnosis and treatment. The costs and resources used in the model are shown in Table 47 and Table 48 below. In the view of the EAG, the sources and assumptions for the unit costs have not been fully reported and therefore we are not able to verify these. We have therefore included this as a scenario, rather than including in the EAG base case.

Table 47 Unit costs for diagnostics and monitoring resources from NHSE model

Imaging / testing unit costs	Unit costs (Company model)	Source	Unit costs (NHSE)	Source
Administration costs	£207.59	NHS Costs – Year 2021/22; Currency code – SB13Z	£565	WD02Z cost uplifted
MRI scan	£197.34	NHS Costs – Year 2021/22; Currency code – RD01A	£191	RZ02Z
Amyloid PET scan	[redacted]	-	£1000	

Imaging / testing unit costs	Unit costs (Company model)	Source	Unit costs (NHSE)	Source
Amyloid PET procedure only	£607.85	NHS Costs – Year 2021/22; Currency code – RN01A	£800	Assumption
Tracer	[redacted]	Assumption based on a draft price for an amyloid radiotracer in the UK	£200	
Blood-based biomarkers[a]	£43.81	NHS Costs – Year 2021/22; Currency code – DAPS02	£43.81	No change
CSF	£406.00	NHS Costs – Year 2021/22; Currency code – HC72A	£580	HC72A
APOE ε4 test	£43.81	NHS Costs – Year 2021/22; Currency code – DAPS02	£250	ApoE4 test
APOE ε4 test outpatient appointment	-	Not included	£200	
APOE ε4 test genetic counselling	-	Not included	£350	WH16B Observation or Counselling

Source: NHSE model costs ('Diagnosis and screening' and 'Treatment' sheets)
APOE, apolipoprotein E; CSF, cerebrospinal fluid; MRI, magnetic resonance imaging; PET, positron emission tomography.
[a] Blood-based biomarkers are not yet available in the UK as such, this cost is an assumption based on the currency code for 'direct access pathology services: histopathology and histology'.

Table 48 Diagnostic testing descriptions and resource use

Test	Base case resource use	NHSE model
CSF[a]	90%	85%
Amyloid PET scan[a]	10%	15%
MRI scan	75%	100%
APoE ε4 test	100%	100%
APOE ε4 test outpatient appointment	0%	100%

Test	Base case resource use	NHSE model
APOE ε4 test genetic counselling	0%	50%

Source: CS Table 38 and NHSE model costs ('Diagnosis and Screening' sheet).
APOE, apolipoprotein E; CSF, cerebrospinal fluid; MRI, magnetic resonance imaging; PET, positron emission tomography.
[a] A factor of 2 is applied to these proportions to account for patients who receive a diagnostic test but do not go on to receive treatment with donanemab.

The results of the NHSE model costs scenario are shown in Table 49. The ICER increases to £178,659 per QALY. We note that most of this increase is due to the increase in drug administration costs. We note that the reference cost code WD02Z for administration costs in NHS reference costs 21/21[104] is £660.10. Using this cost increases the ICER to £185,761 per QALY.

Table 49 Scenario using NHSE model costs and resources

Scenario	Treatment	Total costs	Total QALYs	ICER £/QALY
EAG base case	Donanemab	[redacted]	3.89	£149,531
	BSC	[redacted]	3.67	
NHSE model scenario	Donanemab	[redacted]	3.89	£178,773
	BSC	[redacted]	3.67	
NHSE model scenario with administration cost of £660	Donanemab	[redacted]	3.89	£185,875
	BSC	[redacted]	3.67	

BSC, best supportive care; EAG, External Assessment Group; ICER, incremental cost-effectiveness ratio; NHSE, National Health Service of England; QALY, quality-adjusted life-years.

6.4 Conclusions on the cost effectiveness evidence

The company developed a model to estimate the cost-effectiveness of donanemab compared to best supportive care for patients with mild cognitive impairment or mild dementia caused by Alzheimer's disease. The EAG considers the structure of the model to be reasonable, appropriate and consistent with previous cost-effectiveness models of donanemab. Natural history transition probabilities were obtained from US NACC UDS data. The hazard ratio for mortality was assumed to be the same for all disease severity stages. Treatment effectiveness of donanemab was applied in the model as a hazard ratio for disease progression based on data from the TRAILBLAZER-ALZ 2 trial. The full treatment effect of donanemab was retained for five years after stopping treatment (except for patients

discontinuing due to adverse events or progression to severe disease) and then gradually waned for another five years. Patient and caregiver utilities were applied for each health state of the model. The company's model did not meet the requirements of NICE's reference case for the estimation of utilities and health state care costs (see Table 28 above). The company's base case shows an ICER of £19,736 per QALY for donanemab versus BSC, including a PAS discount for donanemab.

The EAG disagrees with several of the assumptions in the company's model. Our preferred assumptions include:

1. **Treatment duration of donanemab**: No patients discontinue before 18 months due to reaching amyloid clearance.
2. **Risk of residential care**: Annual probabilities of moving to residential care from the GERAS study[84] (see Table 32).
3. **Mortality risk for Alzheimer's disease**: Hazard ratios are assumed to increase with progression of disease and were taken from Crowell et al[1] (see Table 33). **(Key issue)**
4. **Long-term treatment effect**: Full treatment effect retained for one year after stopping treatment and then waned for the following 2.5 years. **(Key issue)**
5. **Patient utility:** Use utility values from GERAS study,[76] rather than Landeiro et al.[94] (see Table 36). **(Key issue)**
6. **Caregiver disutility**: Caregiver utilities taken from the GERAS study,[92] rather than the company's vignettes[93; 95] (see Table 37). **(Key issue)**
7. Number of caregivers per patient: Reduced from 1.8 to 1.
8. **Health care resource use:** Use health state costs from Wittenberg et al.,[107] which does not include unpaid care costs. We do not apply terminal care costs to avoid double counting (as these are included in the Wittenberg et al. estimates).
9. **Outpatient consultations:** We include an outpatient consultation for the diagnostic process and one consultation per model cycle for the first 18 months.

Incorporating the EAG preferred assumptions, the ICER increase to £149,531 per QALY for donanemab vs best supportive care. The model results are most sensitive to changing the assumptions for how long the treatment effect lasts, using an alternative source for the caregiver disutilities and the source of the mortality hazard ratios.

We did not explore the use of a hazard ratio combining the results of both TRAILBLAZER-ALZ trials for iADRS and CDR-SB outcomes as the company declined to conduct a meta-analysis in their response to clarification question A18.

7 SEVERITY

In response to clarification question B33, the company acknowledged that caregivers' disutility should not have been included in the calculation of the severity modifier. They recalculated the QALY shortfall and state that excluding the carer quality of life, donanemab does not meet the criteria for a severity modifier.

The EAG calculated the QALY shortfall for donanemab by using the online tool published by Schneider et al.[109] We used the sex distribution (55% female, weighted average of MCI and mild populations) and starting age (73 years) from the TRAILBLAZER-ALZ 2 trial. The absolute QALY shortfall for donanemab in the company's revised base case is below 12 and the proportional QALY shortfall is less than 85% (see Table 50 below). We also calculated the absolute and proportional QALY shortfall using the EAG base case and obtained similar results to the company's revised base case (Table 50), i.e., the thresholds for severity are not met, so we agree that there is not a case for applying a multiplier for disease severity. The EAG agrees with the company's conclusion, and we have removed the severity modifier in our base case analysis.

Table 50 QALY shortfall analysis

	Expected total QALYs for the general population	Total QALYs that people living with a condition would be expected to have with current treatment	Absolute QALY shortfall	Proportionate QALY shortfall
Company's revised base case	8.04	4.09	3.95	49.15%
EAG base case	8.04	3.82	4.22	52.51%

Source: Schneider et al. 2021[109]
QALYs, quality adjusted life-years.

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9 APPENDICES

Appendix 1 EAG critique of the methods of the company's clinical effectiveness review

Table 51 shows the EAG's critique of the company's SLR of the clinical efficacy and safety of donanemab and other disease-modifying therapies for Alzheimer's disease.

Table 51 EAG appraisal of systematic review methods

Systematic review components and processes	EAG response (Yes, No, Unclear)	EAG comments
Was the review question clearly defined using the PICOD framework or an alternative?	Yes	The aim of the SLR was to identify evidence on the efficacy and safety of disease-modifying therapies for treating early symptomatic Alzheimer's Disease (CS Appendix B, section B.1). The PICOS framework was used to develop the search strategies and specify the study eligibility criteria (CS Appendix B, section B.1).
Were appropriate sources of literature searched?	Yes	Sources searched included Embase, MEDLINE and MEDLINE In Process, and Cochrane CENTRAL and CDSR, conferences, websites of international HTA agencies, clinical trial registries and reference lists of systematic reviews (CS Appendix B, section B.1.2.1).
What time period did the searches span and was this appropriate?	Yes	Searches were limited to sources published between 2010 to August 2023 (the original search was conducted in June 2023 and updated in August 2023; CS Appendix B, sections B.1 and B.1.2.1). Conference proceedings from meetings held between 2021 and 2023 were searched (CS Appendix B, section B.1.2.1). The timespan

Systematic review components and processes	EAG response (Yes, No, Unclear)	EAG comments
		appears appropriate for capturing relevant studies of donanemab.
Were appropriate search terms used and combined correctly?	Unclear	The search terms are provided in CS Appendix B, section B.1.2.2. The EAG notes that no subject headings were used for Alzheimer's disease and no explanation is given for this. Other than this, we do not have any concerns about the search terms used for the clinical effectiveness searches.
Were inclusion and exclusion criteria specified? If so, were these criteria appropriate and relevant to the decision problem?	Yes	The study inclusion and exclusion criteria are reported in CS Appendix B, Table 1. The eligibility criteria match the decision problem (CS Table 1), with the exception that the intervention criteria are wider than the decision problem, as other disease-modifying pharmacological treatments in addition to donanemab could be included in the review. The EAG does not view this as a concern, as the eligibility criteria would capture donanemab studies. Items published before 2010 that were not included in a previous systematic literature review conducted for TA217[110] were excluded, as the company expected none of these studies to be relevant, especially as this timeframe preceded disease-modifying treatment clinical trials in Alzheimer's disease (clarification response A2). We believe this is reasonable.
Were study selection criteria applied by two or more reviewers independently?	Yes	CS Appendix B, section B.1.3 states that two independent reviewers carried out title and abstract and full text screening.

Systematic review components and processes	EAG response (Yes, No, Unclear)	EAG comments
Was data extraction performed by two or more reviewers independently?	Yes	CS Appendix B, section B.1.4 states that data extraction was carried out by one reviewer, and another validated the data entries to ensure accuracy and consistency. Whilst it is not clear if the reviewers operated independently of each other, the EAG views this as an acceptable approach.
Was a risk of bias assessment or a quality assessment of the included studies undertaken? If so, which tool was used?	Yes	CS Appendix B, section B.1.5 states that the company used the Cochrane Risk of Bias Tool 2.0[61] to assess the risk of bias of the included studies.
Was risk of bias assessment (or other study quality assessment) conducted by two or more reviewers independently?	Yes	CS Appendix B, section B.1.5 states that one reviewer carried out the risk of bias assessments, and another verified them. As above, whilst it is not clear if the reviewers operated independently of each other, the EAG views this as an acceptable approach.
Is sufficient detail on the individual studies presented?	Yes	The studies included in the review are listed in CS section B.2.2. Details of the trial design, methodology, participant baseline characteristics, statistical methods and the neuropsychological tests used in the key trial included in the review (TRAILBLAZER-ALZ 2) are provided in CS sections B.2.3.2, B.2.3.3, B.2.3.4, B.2.4, and B.2.3.1, respectively. Trial results are provided in CS section B.2.6. Details about another relevant included trial (TRAILBLAZER-ALZ), which did not inform the company's

Systematic review components and processes	EAG response (Yes, No, Unclear)	EAG comments
		cost-effectiveness analyses, are provided in CS Appendix I, with the results of the company's risk of bias assessment of this study reported in CS Appendix B, section B.3, Table 8.
If statistical evidence synthesis (e.g. pairwise meta-analysis, ITC, NMA) was undertaken, were appropriate methods used?	N/A	No statistical evidence synthesis was included in the CS. In clarification question A18, the EAG asked the company to explain why a meta-analysis of the TRAILBLAZER-ALZ and TRAILBLAZER-ALZ 2 trials was not conducted and requested that they carried out one. The company replied that in their opinion the two trials were too heterogeneous to combine in a meta-analysis, and therefore the company did not carry out a meta-analysis as requested (clarification responses A18a and A18b).

Source: EAG created table, using information supplied in CS sections B.2.2, B.2.3.1, B.2.3.2, B.2.3.3, and B.2.4, CS Table 1, and CS Appendices B.1, B.1.2.1, B.1.2.2, B.1.3, B.1.4, B.1.5, and B.3.
CDSR, Cochrane Database of Systematic Reviews; CS, company submission; EAG, External Assessment Group; N/A, not applicable; PICOS, Population, Intervention, Comparison, Outcomes and Study; SLR, systematic literature review.

Appendix 2 Company and EAG risk of bias assessments

The company and the EAG's risk of bias assessments of the TRAILBLAZER-ALZ and TRAILBLAZER-ALZ 2 trials are shown in Table 52.

Table 52 Company and EAG risk of bias assessments for the TRAILBLAZER-ALZ and TRAILBLAZER-ALZ 2 RCTs

		TRAILBLAZER-ALZ	TRAILBLAZER-ALZ 2
1. Bias arising from the randomisation process	Company	Low	Low
	EAG	Low	Low
EAG comment: **TRAILBLAZER-ALZ** and **TRAILBLAZER-ALZ 2**: [redacted].[30; 111] In both trials, baseline characteristics were well-balanced between treatment arms [CS Table 7 and Mintun et al. (2021)[63]].			
2. Bias due to deviations from intended interventions	Company	Some concerns	Some concerns
	EAG	Low	Low
EAG comment: **TRAILBLAZER-ALZ** and **TRAILBLAZER-ALZ 2**: The company noted some concerns about the potential for study unblinding due to ARIA events in both trials. We agree that this potential exists, but the EAG did not find evidence to suggest that potential unblinding led to deviations from the intended interventions that would be inconsistent with what would happen in clinical practice. Instead, we are more concerned about the impact of this on outcome assessment (please see point 4 below). An appropriate analysis was used to assess the effect of assignment to intervention ([redacted][112] and modified intention-to-treat (mITT), in TRAILBLAZER-ALZ and TRAILBLAZER-ALZ 2, respectively).			
3. Bias due to missing outcome data	Company	Low	Low
	EAG	Some concerns	Some concerns
EAG comment: **TRAILBLAZER-ALZ**: Overall, 28.2% (37/131) of the participants in the donanemab arm and 25.4% [a] (32/126) of the participants in the placebo arm discontinued the trial.[63] [redacted] of participants in the donanemab arm and [redacted] of participants in the placebo arm had missing outcome data on the LS mean change from baseline outcome at			

		TRAILBLAZER-ALZ	TRAILBLAZER-ALZ 2
Week 76 (percentages calculated by the EAG).[112] An MMRM analysis of this outcome was conducted and this type of analysis assumes that data are missing at random;[113] however as the European Medicines Agency Guideline on Missing Data in Confirmatory Clinical Trials[114] states it is likely that some data are missing not at random. It is possible that the size of the treatment effect could be overestimated when an MMRM analysis is used and not all data are missing at random. We note that the patient flow diagram in the trial paper shows that 20/37 (54.1%) of the participants assigned to donanemab who discontinued the trial did so due to adverse events compared to 6/32 (18.8%) of the participants assigned to placebo who discontinued the trial and 8/32 (25%) of those in the placebo group who discontinued the trial did so for 'other reasons' in comparison to only 3/37 (8.1%) who had 'other reasons' for discontinuing the trial in the donanemab arm (percentages calculated by the EAG).[63] These differences in the reasons for missing data between the trials arms may be an indication that missingness is related to the outcome's true value. The Statistical Analysis Plan that the company provided [redacted]. **TRAILBLAZER-ALZ 2**: 26.9% (231/860) of the participants randomised to donanemab and 19.7% (173/876) of the participants randomised to placebo discontinued the trial by Week 76 (percentages calculated by the EAG).[30] The trial paper shows that 50/231 participants (21.6%) assigned to donanemab who discontinued the trial did so due to adverse events compared to 21/173 participants (12.1%) assigned to placebo who discontinued the trial (percentages calculated by EAG).[30] Other reasons for missing data were similar between arms. Again, as the proportion of participants with this reason for missing outcome data differs between the donanemab and placebo arms, this suggests that missingness may be related to the outcome's true value. In response to clarification question A16 the company describe sensitivity analyses for the ITT population conducted under the missing at random assumption and conducted with a missing not at random assumption. Results from these analyses are provided for the CDR-SB (MMRM analysis) and the iADRS (NCS2 analysis) outcomes (response to clarification question A16, Table 8). In comparison to the primary mITT analyses the least-squares mean change difference [redacted] under the missing at random assumption analysis based on the ITT population whereas with the missing not at random assumption the least-squares mean change difference [redacted].			
	Company	Low	Low

		TRAILBLAZER-ALZ	TRAILBLAZER-ALZ 2
4. Bias in measurement of the outcome	EAG	High	High
EAG comment: **TRAILBLAZER-ALZ** and **TRAILBLAZER-ALZ 2**: Both trials were double-blind, but as acknowledged in the trial papers (Mintun et al.[63] and Sims et al.,[30] respectively) and as acknowledged by the company above (point 2), there was potential for unblinding (i.e. for participants, their supporters or trial staff to become aware of or guess they had been assigned to donanemab) due to ARIA events and infusion-related reactions. Rates of ARIA events and infusion-related reactions were higher in the donanemab treated patients than in those who received placebo in the trials (sources: trial paper for TRAILBLAZER-ALZ[63] and CS Table 14 for TRAILBLAZER-ALZ 2). For example, in TRAILBLAZER-ALZ, 26.7% of donanemab participants had ARIA-E compared to 0.8% of placebo participants, and in TRAILBLAZER-ALZ 2, 24.0% of donanemab participants had ARIA-E compared to 1.9% of placebo participants. CDR raters were blinded to adverse events information in TRAILBLAZER-ALZ 2.[30] However, the CDR is completed through a semi-structured interview with the patient and their supporter (see section 3.2.2.1.1.2), and it is unclear how patients and supporters would have been prevented from becoming aware of treatment assignment when these adverse events occurred in both trials. Patient and supporter answers might therefore have been affected by knowledge of the intervention.			
5. Bias in selection of the reported result	Company	Low	Low
	EAG	Some concerns	Low
EAG comment: **TRAILBLAZER-ALZ**: [redacted] **TRAILBLAZER-ALZ 2**: The EAG has reviewed the trial CSR[31] and SAP[116] and have not identified any information to suggest that the outcome was not analysed in accordance with pre-specified plans.			
6. Overall bias judgement	Company	Some concerns	Some concerns
	EAG	High	High
EAG comment: **TRAILBLAZER-ALZ**: We identified a high risk of bias due to the potential impact of unblinding due to adverse events on measurement of the outcome as well as some			

		TRAILBLAZER-ALZ	TRAILBLAZER-ALZ 2
concerns about bias due to differences between treatment arms in the reasons for missing data and some concerns about bias in relation to selection of the reported result. These considerations lead to an overall rating of a high risk of bias for this study. **TRAILBLAZER-ALZ 2**: The potential impact of participants and their supporters becoming aware of the participants' treatment assignment due to adverse events on measurement of CDR-SB outcome presents in our opinion a high risk of bias and we also have concerns about bias due to missing data. These concerns lead to an overall judgement of a high risk of bias for this study.			

Source: Table created by the EAG using information available in CS section B.2.5, CS Table 7, CS Appendix B.3, the trials' protocols, statistical analysis plans, and clinical study report, and the trial papers.[30; 63]
APOE ε4, apolipoprotein E genotype e4 allele; ARIA, amyloid-related imaging abnormalities; ARIA-E, amyloid-related imaging abnormalities of oedema/effusion; CDR, Clinical Dementia Rating scale; CDR-SB, Clinical Dementia Rating – Sum of Boxes; CS, company submission; EAG, External Assessment Group; FAS, full analysis set; LS, least-square; mITT, modified intention-to-treat; MMRM, mixed model repeated measures; SAP, statistical analysis plan.
[a] Reported in the trial paper as 25.6%, but we calculate 25.4%.[63]

Appendix 3 Characteristics and model inputs of the cost-effectiveness studies by Ross et al. 2022 and Lin et al. 2022

Table 53 Main characteristics and model inputs of the cost-effectiveness studies by Ross et al. 2022 and Lin et al. 2022

Characteristics	Ross et al. 2022[69]	Source	Lin et al. 2022[70]	Source
General				
Discount rate	3% for costs and outcomes	-	3% for costs and outcomes	-
Time horizon	Lifetime	-	Lifetime	-
Perspective of analysis	US healthcare sector and societal perspectives	-	US healthcare sector and modified societal perspectives	-
Model structure	State transition model with 1-month cycle length, categorised by age and AD clinical stage defined by the CDR scale (MCI, Mild, Moderate and Severe).	-	Markov model with 1-year cycle length, comprised by five health states: MCI due to AD, mild AD, moderate AD, severe AD and death.	Lin et al. 2021
Population (baseline)				
Initial age, mean (SD)	72.5 (5.5) years	Mintun et al. 2021	72 years	Weighted average based on Mintun et al. 2021 and van Dyck et al. 2022
Female, %	-	-	52%	
Distribution across MCI due to AD and mild AD dementia	MCI due to AD: 65% Mild AD dementia: 35%	Mintun et al. 2021	MCI due to AD: 55% Mild AD dementia: 45%	Potashman et al. 2020
Proportion in community setting, %	-	-	92%	Johnson, 2019
Natural history	Monthly transition probabilities		Annual transition probabilities	

Characteristics	Ross et al. 2022[69]	Source	Lin et al. 2022[70]	Source
MCI to mild AD	0.007	Mitchell et al. 2009	23%	Potashman et al. 2020
Mild AD to MCI	-	-	3%	Potashman et al. 2020
Mild to moderate AD	0.016	Spackman et al. 2012	35%	Potashman et al. 2020
Mild to severe AD	-	-	4%	Potashman et al. 2020
Moderate to mild AD	-	-	3%	Potashman et al. 2020
Moderate to severe AD	0.026	Spackman et al. 2012	42%	Potashman et al. 2020
Severe to moderate AD	-	-	2%	Potashman et al. 2020
Treatment effects				
Disease progression, HR of donanemab versus placebo	0.68 (95% CI, 0.44-0.99)	Mintun et al. 2021 (based on iADRS score)	0.69	van Dyck et al. 2022
Amyloid reduction on PET imaging	27% at 6 months 55% at 12 months	-	60% at 12 months 68% at 24 months	-
AD-related mortality	Hazard ratio		Relative risk	
MCI	1.61	Stokes et al. 2020	1.82	Andersen et al. 2010
Mild	2.23	Villarejo et al. 2011	2.92	Andersen et al. 2010
Moderate	3.10	Villarejo et al. 2011	3.85	Andersen et al. 2010
Severe	4.98	Villarejo et al. 2011	9.52	Andersen et al. 2010
Progression to residential care			Annual probabilities	
MCI	-	-	2.4%	Lin et al. 2022 Table E6
Mild	-	-	3.8%	Neumann et al. 1999
Moderate	-	-	11%	Neumann et al. 1999
Severe	-	-	25.9%	Neumann et al. 1999
Adverse events				

Characteristics	Ross et al. 2022[69]	Source	Lin et al. 2022[70]	Source
ARIA probability with donanemab	39% (16% were symptomatic) Assumption: 50% of ARIA cases by month 3; 40% in months 4 to 12; and 10% in months 13 to 24.	Mintun et al. 2021	36.4% (5.2% symptomatic)	Weighted average based on Mintun et al. 2021 and TRAILBLAZER 4
Discontinuation due to AEs	-	-	30.5%	Mintun et al. 2021
Utility[a]				
MCI due to AD	0.73	Newmann et al. 2000	Community: -0.17 Long-term care: -0.17	Neumann et al. 1999
Mild AD	0.69	Newmann et al. 2000	Community: -0.22 Long-term care: -0.19	Neumann et al. 1999
Moderate AD	0.53	Newmann et al. 2000	Community: -0.36 Long-term care: -0.42	Neumann et al. 1999
Severe AD	0.34	Newmann et al. 2000	Community: -0.53 Long-term care: -0.59	Neumann et al. 1999
Caregiver utilities	No caregiver utilities due to data suggesting that current measures of caregivers' health-related quality-of-life do not vary markedly with dementia severity		MCI due to AD: -0.03 Mild AD: -0.05 Moderate AD: -0.08 Severe AD: -0.10	Neumann et al. 1999 adjusted for AD severity based on Mesterton et al. 2010
AEs utility decrements	Symptomatic ARIA: 0.065 lasting 3 months	Pitkala et al. 2008	-0.14 for a duration of 12 weeks (disutility for headache)	Xu et al. 2011
Resource use				
MRI (treatment with donanemab)	Two per year	-	Four per year during the first year	-
PET scan (treatment with donanemab)	Two per year	-	Two in the first year and one in the second year; For patients that achieved amyloid clearance and not yet	-

Characteristics	Ross et al. 2022[69]	Source	Lin et al. 2022[70]	Source
			moderate AD dementia, one PET per year.	
Managing ARIA events	1 additional 30-minute physician visit and monthly MRIs until resolution with a mean duration of 3 months.	-	Three MRIs (one per month for 3 months)	FDA 2020
ARIA-related hospitalisation duration	11.6 days	-	-	-
Results				
LYs	-	-	Supportive care: 5.53 Donanemab: 5.96 Incremental: 0.43	-
QALYs	Standard of care: 4.948 Donanemab: 5.356 Incremental: 0.408	-	Supportive care: 2.89 Donanemab: 3.38 Incremental: 0.49	-
Costs	Standard of care: $118,000 Donanemab: $196,700 Incremental: $78,700	-	Supportive care: $339,000 Donanemab: $405,000 Incremental: $66,000	-
ICER for donanemab versus comparator	$193,000/QALY	-	$139,000/QALY	-

Source: Ross et al. 2022[69], and Lin et al. 2022.[70]
AD, Alzheimer disease; AEs, adverse events; CDR, Clinical Dementia Rating Scale; CDR-SB, Clinical Dementia Rating Scale Sum of Boxes; HR, hazard ratio; iADRS, integrated Alzheimer disease rating scale; ICER; incremental cost-effectiveness ratio; MCI, mild cognitive impairment; PET, positron emission tomography; QALYs, quality adjusted life years.
[a] In the study by Lin et al. 2022, the utility inputs are disutilities.

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External Assessment Group Report commissioned by the NIHR Evidence Synthesis Programme on behalf of NICE

Donanemab for treating mild cognitive impairment or mild dementia caused by Alzheimer's disease [ID6222]

Addendum 1 – EAG base case probabilistic results

Produced by	**Southampton Health Technology Assessments Centre (SHTAC)**
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Date completed	12/06/24

[redacted]

In this addendum, we present the probabilistic results for the EAG base case, as requested by NICE on 6th June 2024. Donanemab has additional costs of £33,542 and additional QALYs of 0.222 compared to BSC and an ICER of £151,133 per QALY. The probabilistic results are similar to the deterministic results presented in the EAG report.

Table 1 EAG base case probabilistic results with PAS for donanemab

Treatment	Total costs (£)	Total Life years	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER versus baseline (£/QALY)
Donanemab	[redacted]	6.35	3.83	£33,542	0.222	£151,133
BSC	[redacted]	6.14	3.61	-	-	-

BSC, best supportive care; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year

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Donanemab for treating mild cognitive impairment or mild dementia caused by Alzheimer's disease [ID6222]

Addendum 2 – EAG critique of the company's EAG Report Issue 4 Additional Analyses

Produced by	**Southampton Health Technology Assessments Centre (SHTAC)**
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Date completed	12/06/2024

1 INTRODUCTION

In this addendum we critique a document submitted by the company titled 'EAG Report Issue 4 – Additional Analyses'. This was submitted in response to the EAG's Key Issue 4: Risk of bias associated with the TRAILBLAZER-ALZ trials and the potential impact on the measurement of the treatment effect.

We raised Key Issue 4 because we had concerns that both the TRAILBLAZER-ALZ trials were at a high risk of bias for the key secondary outcome of risk of participants progressing on the Clinical Dementia Rating Sum of Boxes (CDR-SB) at Week 76 which informs the economic model. In particular, and as acknowledged in the published trial papers[1,2] and the company submission, amyloid-related imaging abnormality (ARIA) events and infusion-related reactions could have caused participants, their supporters or trial staff to believe that they had been assigned to donanemab, which would mean some unblinding could occur during the trials. To gain insight into any impact that ARIA and/or infusion-related reactions may have had, we asked the company to provide sensitivity analyses of the hazard ratio for disease progression over time to week 76 as measured by the CDR-SB in which participants who experience ARIA or infusion-related reactions or both are censored after the first occurrence (if they have not already experienced disease progression).

2 EAG CRITIQUE OF COMPANY ADDITIONAL ANALYSES

The company conducted sensitivity analyses for the TRAILBLAZER-ALZ 2 population which were based on the original analysis reported in CS section B.2.6.5 with the additional specification that participants were censored at their first occurrence of ARIA or infusion-related rection if they had not already experienced disease progression. The results from the sensitivity analyses are reported for two outcomes, the CDR-SB and the Integrated Alzheimer's Disease Rating Scale (iADRS). The company state that in these sensitivity analyses the number of events (due to the censoring of participants at first occurrence of ARIA or infusion-related reaction) drops more in the donanemab arm than in the placebo arm, which is to be expected (in TRAILBLAZER-ALZ 2 ARIA E occurred in 24.0% of participants in the donanemab group and 1.9% in the placebo group, ARIA-H occurred in 19.7% of participants in the donanemab group and 7.4% in the placebo group). The company states that the impact of the additional censorings is limited because they occur early in the treatment period. The company has not provided a Figure (similar to CS Figure

10) to show the number at risk at each time point, but we agree that infusion-related reactions would be expected to occur early in the treatment period. Furthermore, based on information presented in the clinical study report (CSR) for TRAILBLAZER 2 (CSR section 5.2.1.4.1.2.2 and CSR Figure AACI.5.24), we agree that ARIA events would predominantly occur early in the treatment period.

The company present their sensitivity results for the TRAILBLAZER-ALZ 2 trial in Table 1 of their 'EAG Report Issue 4 – Additional Analyses' document and compare these to the results from the original analyses. For the CDR-SB the hazard ratio for the sensitivity analysis with ARIA and infusion-related reaction censoring is [redacted] than the hazard ratio from the original analysis. For the iADRS outcome, the hazard ratio from the sensitivity analysis is [redacted] than the hazard ratio from the original analysis. The company did not provide updated economic model results using the hazard ratios from the sensitivity analysis stating that, due to the similarity in the hazard ratio results, it was not expected that the economic model results would meaningfully change. We agree this is the case when using the CDR-SB hazard ratio from the sensitivity analysis in the economic model, but we disagree with the company when the iADRS hazard ratio from the sensitivity analysis is used in the economic model because the ICER [redacted] which we consider to be a meaningful change.

3 REFERENCES

1. Mintun MA, Lo AC, Duggan Evans C, et al. Donanemab in Early Alzheimer's Disease. *N Engl J Med* 2021;384(18):1691-704.
2. Sims JR, Zimmer JA, Evans CD, et al. Donanemab in Early Symptomatic Alzheimer Disease: The TRAILBLAZER-ALZ 2 Randomized Clinical Trial. *JAMA* 2023(330):512-27.

Single Technology Appraisal

Donanemab for treating mild cognitive impairment or mild dementia caused by Alzheimer's disease [ID6222]

EAG report – factual accuracy check and confidential information check

"Data owners may be asked to check that confidential information is correctly marked in documents created by others in the evaluation before release." (Section 5.4.9, NICE health technology evaluations: the manual).

You are asked to check the EAG report to ensure there are no factual inaccuracies or errors in the marking of confidential information contained within it. The document should act as a method of detailing any inaccuracies found and how they should be corrected.

If you do identify any factual inaccuracies or errors in the marking of confidential information, you must inform NICE by **5pm on Friday 26 April 2024** using the below comments table.

All factual errors will be highlighted in a report and presented to the appraisal committee and will subsequently be published on the NICE website with the committee papers.

Please underline all confidential information, and information that is submitted as [redacted] should be highlighted in turquoise and all information submitted as '[redacted]' in pink.

Issue 1 Identified Factual Issues

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 16; Section 2.2.1.3, where the EAG states: *'One of our clinical experts highlighted that there are no drugs licensed for MCI in the UK and the licensed drugs for mild to moderate dementia due to Alzheimer's disease only have symptomatic effects (i.e. they do not improve symptoms, but rather delay symptom progression).'*	The statement should be updated to: *'One of our clinical experts highlighted that there are no drugs licensed for MCI in the UK and the licensed drugs for mild to moderate dementia due to Alzheimer's disease only have symptomatic effects (**i.e. they improve symptoms, but do not delay symptom progression**).'*	The explanatory information given in brackets is incorrect, treatments with only symptomatic effects will improve symptoms but will not delay symptom progression.	We agree with the company and the text has been updated as suggested by the company.
Page 37 and 38; Section 3.2.1.1, Table 6 Comparison of TRAILBLAZER-ALZ and TRAILBLAZER-ALZ 2 study designs, footnote b states: *'There was an immunogenicity and safety follow-up period. The length of this is stated as 36 weeks in the trial protocol but* [redacted]	Please update to: *'There was an immunogenicity and safety follow-up period. The length of this is stated as 36 weeks in the trial protocol but* [redacted] *weeks in the CSR. This follow-up is part of the TRAILBLAZER-ALZ LTE (Part B) safety follow-up and TRAILBLAZER-EXT trials.'*	Please note that the trial referred to here is TRAILBLAZER-ALZ LTE (Part B) and was referred to in company submission B.2.10. The company would like to clarify that both TRAILBLAZER-EXT and TRAILBLAZER-ALZ LTE	We have updated our table footnote along the lines suggested by the company. We have incorporated the information provided by the company on the TRAILBLAZER-EXT and TRAILBLAZER-ALZ LTE (Part B) follow-ups which was not clearly presented

weeks in the CSR. It is not clear if this is the TRAILBLAZER-LTE (Part B) that is listed (with no reference given) in CS B.2.9. Additionally, CS sections B.3.1.3 (Model structure) and B.3.2.2 (treatment effect) cite evidence from a TRAILBLAZER-EXT trial and it is not clear if this is the same study as TRAILBLAZER-LTE.'		(Part B) are follow-ups of the phase 2 trial, however, TRAILBLAZER-ALZ LTE (Part B) reported safety only.	in the original company submission. Table 6 footnote b now reads: "There was an immunogenicity and safety follow-up period. The length of this is stated as 36 weeks in the trial protocol but [redacted] weeks in the CSR. This follow-up is part of the TRAILBLAZER-LTE (Part B) safety follow-up (referred to in CS B.2.10) and TRAILBLAZER-EXT[32] trials."
Page 57; Section 3.2.3 states: *'In relation to the TRAILBLAZER-ALZ trial, we additionally identified that the LS mean change from baseline at Week 76 on the CDR-SB outcome was not analysed in full accordance with the planned analysis approach.'*	Please can the EAG update this statement for clarity.	This statement is unclear in its current form.	We have updated this statement to include further detail from the full EAG risk of bias assessment presented in EAR Appendix 2. The text in EAR Section 3.2.3 now reads: "In relation to the TRAILBLAZER-ALZ trial, we additionally identified that the LS mean change

			from baseline at Week 76 on the CDR-SB outcome was not analysed in full accordance with the planned analysis approach [redacted] This led us to consider that there were some concerns regarding bias in selection of the reported result.”
Page 59; Section 3.2.4, Table 12, Methods to account for multiplicity – EAG comment: *‘Appropriate procedures were used in both trials to prevent statistically significant effects being detected by chance.’*	The statement should be updated to: *‘Appropriate procedures were used in both trials **to minimise the risk of** statistically significant effects being detected by chance.’*	This wording does not reflect the approaches taken in the trials. Procedures were used to minimise risk as it was not possible to eliminate or prevent chance entirely.	We agree with the company and the text has been updated as suggested by the company.
Page 132; Section 4.2.11.5, states:	This statement should be attributed to reference 71 in the EAG report: Jones KC, Weatherly H, Birch S, et al. Unit	This statement was incorrectly referenced within the company submission and	We agree with the company and have amended the reference

'In addition, the model included a one-off terminal care cost of £7,274 from Jones et al.[108]'	Costs of Health and Social care 2022. Manual. 2022.	should be update to reflect the correct reference. Lilly apologises for the oversight here.	number to reference 71, as suggested.

Issue 2 Minor Typographical and Grammatical Errors

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 16; Section 2.2.1.3. *'The amyloid cascade hypothesistable 32 posits that…'*	Please update to: '*The amyloid cascade **hypothesis table** 32 posits that…'*	Minor typographical error	No change made. This typographical error is not present in our version of the report that we submitted to NICE (and Table 32 is in section 4.2.7 of our report so is not relevant to the amyloid cascade hypothesis described in section 2.2.1.3).
Page 38; Section 3.2.1. '*in TRAILBLAZER-ALZ 2 only a minimum infusion time of 30 minutes was stated (a minimum of 30 minutes).'*	Please update to ''*in TRAILBLAZER-ALZ 2 only a minimum infusion time of 30 minutes was stated.'*	Minor typographical error	Typographical error corrected as suggested by the company.

Page 41; Section 3.2.1.2. '*We observe that within each trial characteristics are well balanced between arms…*'	Please update to: *'We observe that within each trial characteristics are well balanced* ***between arms****…'*	Minor typographical error	Extra space between words removed.
Page 41; Section 3.2.1.2, Table 8, Row ε2/ε3. The following value is stated *'1/124 (0/8)*.'	Please update to: '*1/124 (0.8)'*	Minor typographical error	Correction made.
Page 45, Section 3.2.2.1. '*Partly reproduced from CS Tables 3, 4 5 and 6, and Appendix I, Table 50'*	Please update to: '*Partly reproduced from CS Tables 3, 4, 5 and 6, and Appendix I, Table 50'*	Minor typographical error	Comma added as suggested by company.
Page 47, Section 3.2.2.1.1.2. *"Scores of 0.5 to 4.0 on the CDR-SB have been found to correspond to a score of 0.5 on the CDR-G, and a score of 4.5 to 9.0 corresponds to a score of 1.0, 9.5 to 15.5 to 2.0, and 16.0 to 18.0 to 3.0 on the CDR-G, respectively"*	Please rephrase this sentence as it is does not make sense in its current form.	This sentence is unclear in its current form.	The concepts in the sentence have been written out in full to improve clarity. This now reads "Scores of 0.5 to 4.0 on the CDR-SB have been found to correspond to a score of 0.5 on the CDR-G, scores of 4.5 to 9.0 on the CDR-SB correspond to a score of 1.0 on the CDR-G, scores of 9.5 to 15.5 on the CDR-SB correspond to

			a score of 2.0 on the CDR-G, and scores of 16.0 to 18.0 on the CDR-SB correspond to a score of 3.0 on the CDR-G.39 ”
Page 50; Section 3.2.2.1.1.6. Section formatting following *‘The reasons for this are:’*	This section appears to be intended to be formatted as 6 bullet points. Please update formatting of this section following *‘The reasons for this are:’* to bullet points, up to and including the point *‘The iADRS appears….’*	Minor formatting error	Bullet point formatting has been reinstated.
Page 50; Section 3.2.2.1.1.6. *‘Our clinical experts indicated that the CDR-SB adequately reflects how cognition and function are assessed in clinical practice and both though it was…’*	Please update to: *‘Our clinical experts indicated that the CDR-SB adequately reflects how cognition and function are assessed in clinical practice and both* ***thought*** *it was…’*	Minor typographical error	Spelling error corrected.
Page 55; Section 3.2.2.3. *‘We define these ARIA events in section 2.2.1.4.’*	Please update to: *‘We define these ARIA* ***events in*** *section 2.2.1.4.’*	Minor typographical error	Extra space between words removed.
Page 65; Section 3.2.5.2, Table 15, LSM change	Please update to: *‘(−0.83 to 0.12;* [redacted] *’*	‘95% CI’ is not required here as it is already defined in the first column	Redundant ‘95% CI’ text removed.

difference for TRAILBLAZER-ALZ: *'(95% CI, −0.83 to 0.12; [redacted]'*			
Page 65; Section 3.2.5.2, Table 15, footnote a: *'a Calculated by the EAG from the SE in the CSR (95% CI comprises the values 1.96xSE either side of the mean)'*	Please update Table 15 to accurately include and attribute footnote 'a' as a citation at the relevant data point or statement where it is intended to apply	Minor typographical error	In our version of the report Table 15 includes the reference to footnote [a] for the 95% CI of the LS mean change for TRAILBLAZER-ALZ in the donanemab and placebo arms. No change made.
Page 81; Section 3.2.5.9, Table 23, first column: *'Participants with ≥1 treatment-emergent AE h'*	Please update to: *'Participants with ≥1 treatment-emergent AE [h]'*	Minor typographical error	Superscript formatting reapplied to 'h'.
Page 84, Section 3.2.5.9.2. *'CS section B.2.9 also reports that…'*	Please update to: *'CS section **B.2.10** also reports that…'*	The section of the CS is reported incorrectly and should be updated.	No change made. In the CS provided via NICE (ID6222 donanemab Eli Lilly Submission v2.0 19032024 IC [CON].docx' the rates of symptomatic ARIA-E and serious ARIA -E in donanemab-treated homozygote APOE ε4 carriers is presented in CS

			section B.2.9. CS Section B.2.10 presents information on ongoing studies.
Page 85; Section 3.2.5.9.2, Table 25. The value reported for the donanemab integrated dataset, noncarrier is '[redacted]'.	Please update to: '[redacted]'	This value is reported incorrectly and should be updated as per Page 72 of the integrated safety summary.	We agree that the value in the CS is incorrect and have updated Table 25 of our report with the value of [redacted] from page 72 of the integrated safety summary.
Page 85; Section 3.2.5.9.2, Table 25. Bullet point following table footnotes	Please remove the erroneous bullet point	Minor typographical error	Bullet point formatting removed.
Page 86; Section 3.4. Bullet point list, third bullet point	Please remove the erroneous bullet point	Minor typographical error	Bullet point formatting removed.
Page 86, Section 3.4. *'We have presented data from the company's phase 2 trial TRAILBLAZER-ALZ alongside that for TRAILBLAZER ALZ 2 in our report because we believe there should be the option in the economic model to draw*	Please update to: *'We have presented data from the company's phase 2 trial TRAILBLAZER-ALZ alongside that for TRAILBLAZER ALZ 2 in our report because we believe there should be the option in the economic model to draw on the combined clinical*	Minor typographical error	'n=' inserted where indicated by the company.

on the combined clinical effectiveness data from these trials (donanemab 131, placebo n=126).'	*effectiveness data from these trials (donanemab **n=**131, placebo n=126).'*		
Page 126; Section 4.2.10.2.2. *'We explore a scenario where we change the number of caregivers from one to 1.8 in the EAG base case and that does not affect the model results in a great extent (section 6.3).'*	Please update to*: 'We explore a scenario where we change the number of caregivers from one to 1.8 in the EAG base case and that does not affect the model results **to** a great extent (section 6.3).'*	Minor typographical error	Text changed as suggested.
Page 126, Section 4.2.10.3. *'…resulting in a utility decrement of -0.112 (value corrected in response to clarification question B20).'*	Please update to: *'…resulting in a utility decrement of **-0.012** (value corrected in response to clarification question B20).'*	Incorrect value reported.	We disagree. We did not change the value as suggested, but we have edited the text in section 4.2.10.3 of our report to make it clearer, as follows: We consider that the value reported by the company in the text response to clarification question B20 (-0.012) is incorrect, as it is different from the value reported in the updated company's model (-0.112).

Page 128, Section 4.2.11.3. *'For instance, in CS section B.1.3.4, it is stated that [redacted] of patients with MCI due to Alzheimer's disease…'*	Please update to: *'For instance, in CS section B.1.3.4, it is stated that [redacted] of patients with MCI due to Alzheimer's disease…'*	Rounding error in the value reported.	We agree. Value amended as suggested.
Page 129; Section 4.2.11.4.1. *'In addition to amyloid testing, patients are also tested for APOE ε04 status.'*	Please update to: *'In addition to amyloid testing, patients are also tested for APOE **ε4** status.'*	Minor typographical error	Text amended as suggested.
Page 129; Section 4.2.11.4.1. *'Service code 400: Consultant-Led Neurology Outpatient Visit104) for this to the cost of the APOE ε04 diagnostic test (£43.81, see Table 40 below) to our base case in section 6.2.)'*	Please update to: *'Service code 400: Consultant-Led Neurology Outpatient Visit104) for this to the cost of the APOE **ε4** diagnostic test (£43.81, see Table 40 below) to our base case in section 6.2.)'*	Minor typographical error	Text amended as suggested.
Page 130; Section 4.2.11.4.3. *'As explained above, we consider that patients would require an outpatient appointment for the*	Please update to: *'As explained above, we consider that patients would require an outpatient appointment for the diagnostic process and added this cost (£221.91) to the cost of APOE **ε4** diagnostic test in our base case.'*	Minor typographical error	Text amended as suggested.

diagnostic process and added this cost (£221.91) to the cost of APOE ε04 diagnostic test in our base case.'			
Page 130; Section 4.2.11.4.3. *'Clinical experts to the EAG are of the opinion that most carriers of an APOE ε04 allele…'*	Please update to: *'Clinical experts to the EAG are of the opinion that most carriers of an APOE **ε4** allele…'*	Minor typographical error	Text amended as suggested.
Page 135; Section 5.1.3. *'The EAG is still unable to replicate the results for scenario 8 - blood-based biomarker test becomes available (rule in) - with the instructions given by the company in their response to clarification question B32.'*	Please update the dashes to en-dashes in the following: *'The EAG is still unable to replicate the results for scenario 8 – blood-based biomarker test becomes available (rule in) – with the instructions given by the company in their response to clarification question B32.'*	Minor typographical error	The dashes have been replaced by brackets.
Page 148; Section 6.3.1. Paragraph beginning: *'NICE requested that we conducted a…'*	Please update formatting of paragraph beginning: *'NICE requested that we conducted a…'* to be consistent with the rest of the document (i.e. paragraph formatting and font size	Minor typographical errors	Paragraph formatting has been amended.

Page 148/149; Section 6.3.1, Table 47	Please update formatting of Table 47 to be consistent with the rest of the document (i.e. font size)	Minor typographical errors	Font size is appropriate. No change necessary.
Page 160; Appendices, Table 51. *'Conference proceedings from meetings held between 2021 and 2023 were searched (CS Appendix B, section B.1.2.1).'*	Please update to: *'Conference proceedings from meetings held between 2021 and 2023 were searched (CS Appendix **B, section** B.1.2.1).'*	Minor typographical error	Extra space between words removed.
Page 161; Appendices, Table 51. *'Other than this, we have do not have any concerns about the search terms used for the clinical effectiveness searches.'*	Please update to: *'Other than this, **we do** not have any concerns about the search terms used for the clinical effectiveness searches.'*	Minor grammatical error	Extra word 'have' deleted.

Overview

Explanation

This page details the Managed Access Team's overall assessment on whether a medicine could be suitable for Managed Access and if data collection is feasible. The feasibility assessment does not provide any guidance on whether a medicine is a cost-effective, or plausibly cost-effective, use of NHS resources. This document should be read alongside other key documents, particularly the company's evidence submission and External Assessment Centre (EAC) report. Further detail for each consideration is available within the separate tabs.

Whilst a rationale is provided, in general the ratings for each area:
Green - No key issues identified
Amber - Either outstanding issues that the Managed Access team are working to resolve, or subjective judgements are required from committee / stakeholders (see key questions)
Red - The managed access team does not consider this topic suitable for a managed access recommendation.

The Managed Access Team may not assess other areas where its work has indicated that topic is not suitable for a managed access recommendation

The feasibility assessment indicates whether the Managed Access team have scheduled to update this document, primarily based on whether it is undertaking actions to explore outstanding issues. There may be other circumstance when an update is required, for example when the expected key uncertainties change or a managed access proposal is substantially amended. In these cases an updated feasibility assessment should be requested from the Managed Access team.

Topic name: **Donanemab for treating mild cognitive impairment or mild dementia caused by Alzheimer's disease**

Topic ID: **6222**
Managed Access Lead: **Steve Norton**
Date of assessment(s): **09/05/2024**

Is Managed Access appropriate - Overall rating	Comments / Rationale
Committee judgement required	There are some ongoing trials which could generate further evidence. Data gathered via the company's proposed studies could provide some useful evidence to resolve some of the identified uncertainties - several uncertainties would not be addressed at all, and some uncertainties only partly addressed. Extensive barriers exist to both implementation and data collection in the NHS (for example, the need to add PET scanning capacity and expertise to the NHS, and the need to ask both primary and secondary care clinicians to record assessment results). No NHS-level data collection is proposed, therefore the most feasible way to gather further data is via the described trials rather than real-world data in clinical practice.

Area	Rating	Comments / Rationale
Is the technology considered a potential candidate for managed access?	Unclear	The treatment is in an area of high unmet need but it is not yet known if the ongoing trials will resolve committee's outstanding uncertainties.
Is it feasible to collect data that could sufficiently resolve key uncertainties?	Unclear	No specific, outstanding uncertainties yet identified.
Can data collection be completed without undue burden on patients or the NHS system*	No	High burden on patients and the system to set up data collection as no RWE data collection is currently in place. This would be made more complex by needing to coordinate across primary and secondary care. A large indication with significant deviations from current practice risks high strain on the system.
Are there any other substantive issues (excluding price) that are a barrier to a MAA*	Yes - Major	Implementation would mean a large change to service provision and would need significant resource to roll out. Any restricted implementation would go against the IMF principles.

* Note NHS England is working on meeting the implementation challenges in this disease area, so there is scope for the RED ratings to change once implementation plans are known. It is acknowledged there will be further discussion needed with NHSE and the manufacturer if a provisional recommendation for MA is made.

Further managed access activity	Rating	Comments / Rationale
pre-committee feasibility assessment update		
pre-committee data collection working group		
pre-committee patient involvement meeting		

Key questions for committee if Managed Access is considered	
1	
2	

Early Identification for Managed Access

Explanation on criteria
These criteria should be met before a technology can be recommended into managed access through the CDF or IMF. To give a 'high' rating, the Managed Access Team should be satisfied that it can be argued that the technology meets the criteria. Companies interested in managed access must engage early with NICE and demonstrate that their technology is suitable for the managed access.

Date agreed with NHSE	10/05/2024

Is the technology a potential candidate for managed access?	
Rating	**Rationale**
Unclear	The treatment is in an area of high unmet need and the published data indicate some promise, but it is not yet known if the ongoing trials will resolve committee's outstanding uncertainties.

IMF prioritisation criteria	Supporting Evidence
Potential to address a high unmet need	No effective treatment for Alzheimer's disease is available through the NHS. As a prevalent, degenerative disease, any treatment would be welcomed by patients and clinicians.
Potential to provide significant clinical benefits to patients	Early-stage evidence (pre-submission) showed some level of efficacy. Whether significant or not will be determined later in the evaluation.
represents a step-change in medicine for patients and clinicians	An effective treatment for AD would be a step-change for patients and clinicians.
new evidence could be generated that is meaningful and would sufficiently reduce uncertainty	The clinical trial programme will continue to produce useful evidence for several years. It is not yet known if this will resolve committee's outstanding uncertainties.

System implementation	Supporting Evidence
The technology has been flagged as a potential IMF candidate to NICE by NHSE horizon scanning	This treatment is being considered as a candidate for a number of potential routes to commissioning.

Uncertainties

Explanation

This page details the Managed Access Team's assessment on whether data collection could sufficiently resolve key uncertainties through further data collection within managed access. The overall assessment is the key judgement from the Managed Access Team.

The Managed Access Team will justify it decision, but broadly it is a matter of judgement on whether the further data collection could lead to a positive NICE decision at the point the technology exits managed access. For this reason individual uncertainties that have a higher impact on the ICER have a greater impact on the overall rating.

Further detail is available on each uncertainty identified primarily informed from a company's managed access proposal, the External Assessment Group (EAG) report, judgements from the NICE Managed Access Team, and where available directly from NICE committee deliberations. The likelihood that data could sufficiently resolve each specific outcome is informed both by the expected primary data source in general (as detailed in the separate tab) and specifically whether the data collected is expected to sufficiently resolve that uncertainty.

Likelihood data collection could sufficiently resolve key uncertainties?	
Rating	**Rationale**
Low	The majority of uncertainties are related to detailed technical decisions to be taken at the committee meeting with additional clinical evidence and will not be impacted or resolved by further data collection. Some uncertainties could be reduced by data collection according to the company's managed access proposal - refer to the Trial Data tab. There is currently no NHS-level data collection proposed.

Key Uncertainties

Issue	Key uncertainty	Company preferred assumption	ERG preferred assumption	Impact on ICER	Data that could sufficiently resolve uncertainty	Proposed primary data source	Likelihood data collection could sufficiently resolve uncertainty	Rationale / Notes
EAG1	Use of acetylcholinesterase inhibitors and memantine	The use of acetylcholinesterase inhibitors in people with MCI due to Alzheimer's disease and the use of memantine in people with either MCI or mild dementia due to Alzheimer's disease is outside the recommendations of NICE NG97. In the company's TRAILBLAZER-ALZ and TRAILBLAZER-ALZ 2 trials approximately 60% of participants received an acetylcholinesterase inhibitor or memantine	Although our clinical experts agreed that some people with MCI due to probable Alzheimer's disease would receive an acetylcholinesterase inhibitor off-label, neither of our experts stated that patients with MCI received memantine in clinical practice. We believe the use of acetylcholinesterase inhibitors and memantine in participants with MCI and the use of memantine for people with mild dementia due to Alzheimer's disease in the TRAILBLAZER-ALZ 2 RCT was higher than estimated in UK clinical practice	Unquantified	Additional data may become available from ongoing European and US studies into long-term effectiveness. EAG said: Additional discussion with clinical experts on the degree to which acetylcholinesterase inhibitors or memantine are used off label for people with MCI due to probable Alzheimer's disease and the degree to which memantine is used off label for people with mild dementia due to probable Alzheimer's disease in clinical practice. Discussion about the potential impact of acetylcholinesterase inhibitors or memantine on measures of cognition and function in people with MCI or mild dementia due to probable Alzheimer's disease.	Clinical expert evidence; further data collection	No further data collection possible / proposed	It is plausible that data collection in clinical practice could produce a more generalisable population in terms of level of acetylcholinesterase inhibitor use, however this has not been proposed. It is not clear that acetylcholinesterase inhibitor effect would be significant, therefore the value in collecting these data are also unclear. The clinical trials and pragmatic RWE studies are not powered to generate estimates of treatment effect within the subgroup of patients who are on / off concomitant treatments. As described in the NICE submission documents, the proportion of patients on concomitant medications was balanced across arms in the TB2 trial. However if this is flagged as an uncertainty within the managed access feasibility assessment, the results of TB-5 (with sites in the UK) may provide a future source of additional evidence that is more generalizable to NHS practice in terms of concomitant symptomatic treatment use

EAG2	Choice of measure of cognition and function for use as the outcome measure of treatment effect in the economic model	EMA guidance published in 2018 on the clinical investigation of medicines for treating Alzheimer's disease states that there is no ideal tool for assessing the efficacy of treatments for dementia and considers a range of tools may be needed to assess treatment efficacy in a trial.	The company's TRAILBLAZER-ALZ and TRAILBLAZER-ALZ 2 trials used five different measures (iADRS, CDR-SB, ADCS-iADL, ADAS Cog13 and MMSE) to measure cognition and/or function (disease progression). The iADRS was the primary outcome of both trials but CDR-SB from the TRAILBLAZER-ALZ 2 trial has been used as the measure of treatment effect in the economic model. On balance, we feel the use of the CDR-SB measure to inform the treatment effect in the company's economic model is appropriate, but we acknowledge that there is value in considering the iADRS as an alternative.	High	EAG said: We requested (clarification question B5c) that the company provide the hazard ratio of progressing to clinically worse health states between donanemab and best supportive care for the iADRS measure and enable its use in the model	Clinical expert evidence	No further data collection possible / proposed	Resolution of this uncertainty does not lend itself to further data collection, due to this being a methodological choice.
EAG3	Analysis of clinical effectiveness results for use in the economic model	The company use a hazard ratio of disease progression (0.62, 95% CI 0.52 to 0.75) based on the CDR-SB outcome as a measure of treatment effect in the economic model that is estimated from the phase 3 TRAILBLAZER-ALZ 2 RCT only. In response to clarification question B5c the company have also provided a hazard ratio of disease progression based on the iADRS outcome from the TRAILBLAZER-ALZ 2 RCT (0.70, 95% CI 0.58 to 0.84). In the phase 2 TRAILBLAZER-ALZ trial the CDR-SB least squares mean change difference between the trial arms was smaller than for the TRAILBLAZER-ALZ 2 trial whereas the least squares mean difference in iADRS score was larger than for the TRAILBLAZER-ALZ 2 trial	The reasons for these differences are not easily explained. They could be a consequence of the slight differences in methodology of the trials and the differences in participant characteristics or they may be a consequence of the variability in the disease course between patients. We believe that, as the patients in both trials are representative of the patients who would receive donanemab in clinical practice, there should be the option to use data from both trials combined in the economic model.	Unquantified	EAG said: We asked the company to conduct meta-analyses for the CDR-SB and iADRS outcomes and asked the company to add an option to use the results from the meta-analyses in the economic model (clarification question A18b and c).	Further company analyses	No further data collection possible / proposed	Resolution of this uncertainty does not lend itself to further data collection, and would require adjustment to the model.

EAG4	Risk of bias associated with the TRAILBLAZER-ALZ trials and the potential impact on the measurement of the treatment effect		The EAG judged both the TRAILBLAZER-ALZ and TRAILBLAZER-ALZ 2 trials to be of an overall high risk of bias. We considered that the potential for participants and their supporters to become aware of participants' treatment allocation due to ARIA events and infusion-related reactions presented a high risk of bias that could affect the measurement of disease progression based on the CDR-SB in the trials, including the HR from the TRAILBLAZER-ALZ 2 trial that is used in the economic model. Additionally, we had some concerns about impact of risk of bias due to missing outcome data on these outcomes, as there were differences in reasons for participants discontinuing the trials between the trials' arms (e.g. adverse events).	Unquantified	EAG said: We would like the company to provide sensitivity analyses of the hazard ratio, using a Cox proportional hazard model, of disease progression over time to week 76 as measured by the CDR-SB in which participants who experience ARIA or infusion-related reactions or both are censored after the first occurrence (if they have not already experienced disease progression), for both the TRAILBLAZER-ALZ and TRAILBLAZER-ALZ 2 trials. We would also like the company to provide economic model scenario analyses using the hazard ratios for the treatment effect when these participants are censored. It would be desirable if the company also conducted the same sensitivity analyses of the hazard ratios with censoring of these participants when the iADRS is used to measure disease progression.	Further company analyses	No further data collection possible / proposed	Resolution of this uncertainty does not lend itself to further data collection, and would require adjustment to the model.
EAG5	Impact of APOE ε4 allele status	Subgroup analyses of adverse events by APOE ε4 allele status indicate that this allele increases the risk of experiencing an ARIA event for people treated with donanemab. People who are homozygous for the APOE ε4 allele have a greater risk of experiencing ARIA events than people who are heterozygous for this allele and both subgroups have a greater risk than people who are not carriers of this allele	One of our clinical experts advised us that due to the risk of ARIA side effects in homozygous carriers of the APOE ε4 allele, these patients should probably not be treated with donanemab. That expert also commented that the potential risks and benefits of treatment would need to be clearly explained to heterozygous APOE ε4 carriers.	Unquantified	EAG said: We do not suggest an alternative approach. As the number of participants in TRAILBLAZER-ALZ 2 who were homozygous for the APOE ε4 allele is comparatively small (n=213 for the iADRS outcome, n=220 for the CDR-SB outcome) it may not be feasible to obtain a hazard ratio of disease progression for this subgroup that could be used in the economic model	Clinical expert evidence; further data collection	Low	It is not clear from the company's managed access proposal that this uncertainty would be reduced by data collection. However, it is feasible that ongoing data collection may provide sufficient evidence to analyse this subgroup of the population. Testing for this allele status is not expected to be part of the marketing authorisation. The clinical trials and pragmatic RWE studies are not powered to generate estimates of treatment effect within the subgroup of patients with different APOE4 ε4 statuses. As described in Section B.3.2.2 of the NICE submission, APOE4 ε4 status is not considered to be a treatment effect modified based on an interaction test completed using the Cox Proportional Hazards model, which was not statistically significant.

EAG6	Hazard ratios for mortality due to Alzheimer's disease	The company's model applies a single hazard ratio for mortality of 2.55 (relative to the general population mortality) for patients with mild, moderate and severe Alzheimer's disease dementia. The mortality for the general population was applied to patients with MCI due to Alzheimer's disease. In response to clarification question B17b, the company updated their model to include the option to vary the mortality hazard ratio according to the severity of Alzheimer's disease and provided hazard ratios from the NACC dataset to inform this new option.	Previous cost-effectiveness studies of donanemab, other published evidence and clinical expert opinion to the EAG suggest that the risk of death should increase with disease severity and therefore we consider that using a single hazard ratio for different health states may not be reflective of the evidence... We do not consider the NACC hazard ratios to be plausible as these were higher for the mild than the moderate health state. The Crowell study reports hazard ratios for mortality for patients at age 80 years that seem a good approximation to the mortality for a population with a starting age of 73 years (the baseline age in the current model).	High	Ongoing studies in the company's managed access proposal could gather relevant data to resolve this uncertainty. EAG said: The EAG prefers to use mortality hazard ratios that increase with increasing disease severity. We use the mortality hazard ratios from the Crowell study for the 80-year-old subgroup in our base case. We explored the uncertainty around this by conducting alternative scenario analyses using different mortality hazard ratios from the literature	TB-ALZ-EXT, TB-REAL OUS, TB-REAL US; Clinical expert evidence	Medium	The company's proposed data sources could contribute to reducing this uncertainty in that they each expect to gather long-term clinical uncertainty and safety evidence.
EAG7	Assumptions on the duration of long-term treatment effect	The company's model assumes that the full treatment effect of donanemab observed during the TRAILBLAZER-ALZ 2 trial period is retained for (a) 3.5 years after stopping treatment and then wanes to zero for the following five years (if patients stop after 18 months or due to amyloid clearance); (b) one year after stopping treatment and then wanes to zero for the following 2.5 years (if patients stop due to adverse events). The company's assumptions are based on two main arguments: the time taken to return to amyloid positivity (>24.1CL) after stopping treatment and the relation between amyloid clearance and clinical benefit.	We acknowledge that the results from TRAILBLAZER-ALZ trial show that patients that discontinued treatment at six months due to amyloid clearance have not returned to amyloid positivity at 18 months, i.e., for one year. Also, there is trial evidence for amyloid targeting therapies which indicates a positive correlation between amyloid clearance and clinical efficacy measures, such as CDR-SB scores. However, we note that there is no evidence on the treatment effect beyond the trial period. The clinical experts advising the EAG consider the company's assumptions to be speculative due to lack of available evidence. The assumptions around the duration of the treatment effect have a considerable impact on the model results.	Unquantified	Ongoing studies in the company's managed access proposal could gather relevant data to resolve this uncertainty. EAG said: The EAG assumes that the full treatment effect is retained for a shorter period of one year after stopping treatment (based on trial evidence) and then wanes for the following 2.5 years (in line with the company's assumption that it takes around 3.5 years for patients to return to amyloid positivity) for patients discontinuing treatment after the fixed duration of 18 months, due to amyloid clearance or due to adverse events.	TB-ALZ-EXT, TB-REAL OUS, TB-REAL US; Clinical expert evidence	High	The company's proposed data sources could contribute to reducing this uncertainty in that they each expect to gather long-term clinical uncertainty and safety evidence.

EAG8	Patient utility values for Alzheimer's disease health states	The company's model uses patient's health state utility values assessed by caregivers using EQ-5D data obtained from the meta-analysis of Landeiro et al. 2020. The pooled estimates of patient utilities combine EQ-5D scores using different countries' value sets	The EAG notes that this is not in line with the NICE Reference Case which states that health state valuations should be derived from a representative sample of the UK population.	Medium	EAG said: The EAG prefers to use EQ-5D scores using a UK value set and therefore we use the proxy-rated patient utilities from the GERAS study in our base case. The GERAS study reported proxy-rated EQ-5D patient utilities assessed by their caregivers for mild, moderate and severe health states. It includes patients from France (n=419), Germany (n=552) and the UK (n=526) but uses the UK value set to calculate patient utilities.	Further discussion on which patient utility estimates are the most appropriate.	No further data collection possible / proposed	Resolution of this uncertainty does not lend itself to further data collection: utility data are usually impractical to obtain during managed access and the company has access to its own EQ-5D data from current sources.
EAG9	Caregiver utility values for Alzheimer's disease health states	The company conducted two vignette studies to derive caregiver utilities using the time trade-off approach, as they argued that the EQ-5D is not sensitive enough to measure the health-related quality of life of caregivers for patients with Alzheimer's disease. The utilities were reported by general population participants.	We note that using time-trade-off utilities reported by general population participants does not meet the criteria for the NICE Reference Case. In our opinion, the company has not provided sufficient convincing evidence to support the use of a different method to derive utilities for use in the economic model	Medium	EAG said: The EAG prefers to use EQ-5D scores directly assessed by caregivers in our base case. The EAG considers that the [GERAS] study utilities meet the NICE Reference Case. As the GERAS study utilities are higher than the utilities for the general population, we have made adjustments to the data used in the model by assuming that caregivers of patients with MCI and mild disease have the same quality of life as the general population based on the age and gender distribution of caregivers in the economic model. For the moderate and severe health states, we adjusted the general population utilities based on the relative decrement between health states observed in the GERAS study. We applied the same utilities regardless of the type of caregiver and the setting where the patient lives. As the evidence is not categorised that way, assumptions would be needed, which would add uncertainty	Further discussion on which caregiver utility estimates are the most appropriate.	No further data collection possible / proposed	Resolution of this uncertainty does not lend itself to further data collection.
MAT1	NHSE resource use	The resource use (patient level, system level) needed to offer this technology to patients is not yet clearly known and is the subject of debate via NHSE.		Unquantified	Real-world evidence from use of technology in NHS would resolve this uncertainty.	RWE from company's planned UK RWE studies; RWE from use in clinical practice under managed access; TB-REAL-OUS	High	Either the company's proposed UK RWE studies, and/or RWE derived from use of donanemab in clinical practice during a period of managed access has potential to gather these data. This would require rigorous monitoring to achieve an accurate and complete data set.

Trial Data

Are there further relevant trial data that will become available after the NICE evaluation?	
Rating	**Rationale/comments**
High	The main comparative study, and several other studies in the clinical trial programme have finished or will finish within the timeline of this evaluation. The committee should be in position to assess all data from these studies and therefore reach a decision based on a relatively complete data set. However, additional data from TRAILBLAZER-ALZ 2, 3 and 5 may develop the evidence significantly in coming years, depending on how data cuts are scheduled. Committee would be able to tie any managed access recommendation to any individual trial or data cut thereof, according to its data needs. Several RWE studies have been designed by the company to address a range of the identified uncertainties. Details are currently redacted for two of the studies. though they are intended to establish long-term clinical data, clinical meaningfulness, long-term safety and resource use. The third will directly resolve costs and resource use in NHS clinical practice, retrospectively.

TRAILBLAZER-ALZ	
Anticipated completion date	Sep-21
Link to clinicaltrial.gov	https://www.clinicaltrials.gov/study/NCT03367403?intr=Donanemab&limit=100&page=1&rank=9
Start date	Dec-17
Data cut presented to committee	
Link(s) to published data	https://www.nejm.org/doi/full/10.1056/NEJMoa2100708
Description of trial	Assessment of Safety, Tolerability and Efficacy of LY3002813 in Early Symptomatic Alzheimer's Disease. Double blinded, versus placebo. Outcomes include change from baseline in Integrated Alzheimer's Disease Rating Scale (iARDS), same against other rating scales including cognitive/behavioural and physiological. Publication asserts 'better composite score' across assessments but more studies needed. N=272

TRAILBLAZER-EXT	
Anticipated completion date	Mar-24
Link to clinicaltrial.gov	https://www.clinicaltrials.gov/study/NCT04640077?intr=Donanemab&limit=100&aggFilters=status:act&rank=3
Start date	Nov-23
Data cut presented to committee	
Link(s) to published data	None found
Description of trial	Open label extension of TRAILBLAZER-ALZ, n=90

TRAILBLAZER-ALZ 2	
Anticipated completion date	Aug-25
Link to clinicaltrial.gov	https://www.clinicaltrials.gov/study/NCT04437511?intr=Donanemab&limit=100&aggFilters=status:act&rank=1

Start date	Jun-20
Data cut presented to committee	
Link(s) to published data	https://jamanetwork.com/journals/jama/article-abstract/2807533
Description of trial	TRAILBLAZER-ALZ 2 is a Phase 3, double-blind, placebo-controlled study to evaluate the safety and efficacy of N3pG antibody (donanemab) in participants with early symptomatic AD (prodromal AD and mild dementia due to AD) with the presence of brain tau pathology. N=1800 (estimated) Following the double-blind 76-week main study period, a double-blind 78-week long-term extension period is added to further evaluate donanemab efficacy and safety over time. Participants from the addendum safety cohort are not eligible for the extension period. Same measurements as for TRAILBLAER-ALZ and also pharmacokinetics (average serum concentration of technology) and number or [sic] participants with anti-donanemab antibodies. Results assert donanemab significantly slowed clinical progression at 76 weeks.

TRAILBLAZER-ALZ 3	
Anticipated completion date	Nov-27
Link to clinicaltrial.gov	https://www.clinicaltrials.gov/study/NCT05026866?intr=Donanemab&limit=100&aggFilters=status:rec&rank=3
Start date	Aug-27
Data cut presented to committee	
Link(s) to published data	None available (one article located about trial design: https://n.neurology.org/content/100/17_Supplement_2/3010)
Description of trial	The main purpose of this study is to evaluate the safety and efficacy of donanemab in participants with preclinical Alzheimer's Disease (AD). Double blind, randomised against placebo. n= 2600 (Estimated) Range of different assessment criteria including time to clinical progression as measured by Clinical Dementia Rating - Global Score (CDR-GS), International Shopping List Test (ISLT), Continuous Paired Associate Learning (CPAL) and others. Pharmacokinetics and antibodies measured as before.

TRAILBLAZER-ALZ 4	
Anticipated completion date	Sep-23
Link to clinicaltrial.gov	https://www.clinicaltrials.gov/study/NCT05108922?intr=Donanemab&limit=100&aggFilters=status:act&rank=2
Start date	Nov-21
Data cut presented to committee	
Link(s) to published data	https://n.neurology.org/content/100/17_Supplement_2/3126
Description of trial	The main purpose of this study is to compare donanemab to aducanumab on amyloid plaque clearance in participants with early symptomatic Alzheimer's Disease (AD). Randomised allocation, open label design. n=200 (estimated) Primary outcomes: percentage of participants who reach complete amyloid clearance on florbetapir F18 positron emission tomography (PET) scan (superiority) on donanemab versus aducanemab in the overall and in the intermediate populations. Other outcomes measured as previously noted for other trials, but now comparatively against aducanemab. Results assert: 'Significantly higher number of participants reached amyloid clearance and amyloid plaque reductions with donanemab vs. aducanumab at 6 months.'

TRAILBLAZER-ALZ 5	
Anticipated completion date	Jun-27

Link to clinicaltrial.gov	https://www.clinicaltrials.gov/study/NCT05508789?intr=Donanemab&limit=100&aggFilters=status:rec&rank=1
Start date	Oct-22
Data cut presented to committee	
Link(s) to published data	None available
Description of trial	TRAILBLAZER-ALZ 5 is a Phase 3, double-blind, placebo-controlled study to evaluate the safety and efficacy of donanemab in participants with early symptomatic AD (prodromal AD and mild dementia due to AD) with the presence of brain tau pathology. n=1500 (estimated) Outcomes equivalent to those recorded in earlier studies.

TRAILBLAZER-ALZ 6	
Anticipated completion date	May-25
Link to clinicaltrial.gov	https://www.clinicaltrials.gov/study/NCT05738486?intr=Donanemab&limit=100&aggFilters=status:rec&rank=2
Start date	Feb-23
Data cut presented to committee	
Link(s) to published data	None available
Description of trial	This study will investigate different donanemab dosing regimens and their effect on the frequency and severity of amyloid-related imaging abnormality - Edema/Effusion (ARIA-E) in adults with early symptomatic Alzheimer's disease (AD) and explore participant characteristics that might predict risk of ARIA. n=800 (estimated) Primary outcomes is percentage of participants with ARIA-E and secondary outcomes are equivalent to earlier studies.

TB-REAL US (AACS)	
Anticipated completion date	CIC
Link to clinicaltrial.gov	-
Start date	-
Data cut presented to committee	-
Link(s) to published data	-
Description of trial	To compare the effect of donanemab plus usual care versus usual care alone on dependence level in participants with early symptomatic AD. Company aims to resolve long-term clinical uncertainty, comfirm clinical meaningfulness, and establish long-term safety

TB-REAL OUS (AACR)	
Anticipated completion date	-
Link to clinicaltrial.gov	-
Start date	-
Data cut presented to committee	-
Link(s) to published data	-
Description of trial	To compare the effect of donanemab and Usual Care versus Usual Care alone on dependence level in participants with early symptomatic AD. PET Sub-study To determine the proportion of participants who reach amyloid clearance, To assess amyloid reduction rates and change in amyloid over time. Company aims to resolve long-term clinical uncertainty, confirm clinical meaningfulness, establish long-term safety and resource use

UK Real World Evidence Studies	
Anticipated completion date	Q4 2026
Link to clinicaltrial.gov	-
Start date	Q4 2024
Data cut presented to committee	-
Link(s) to published data	-
Description of trial	Retrospective study, aiming to: "Generate evidence to inform resource use in health and social care for patients with MCI due to AD and AD dementia" and gather "Patient characteristics, diagnostic experience, and treatment journey in patients with MCI due to AD and AD dementia". This will be the key RWE study resolving uncertainty around cost and resource use in NHS clinical practice. This retrospective RWE study is being fully funded by Eli Lilly and is being carried out in collaboration with a Secure Data Environment (SDE) provider. No collaboration or funding from NHSE is required. Primary Objectives i. Describe the demographic and clinical characteristics of patients diagnosed with mild cognitive impairment (MCI) and mild, moderate and severe AD ii. Estimate the total health-care resource use (HCRU) incurred by AD patients within each stage of disease, stratified by direct healthcare cost, social care cost and informal care cost (if available) iii. To estimate the impact of a slowing of disease progression in terms of resource use, costs, dependency and care level Secondary Objectives The secondary objective is to investigate the association between baseline patient characteristics and HCRU at the later stage of AD. Exploratory Objectives The exploratory objective is to estimate the impact of a slowing of disease progression in terms of resource use, dependency and care level

Data collected in clinical practice

Is RWE data collection within managed access feasible?	
Overall Rating	**Rationale/comments**
Low	There are no current robust, NHSE-wide RWE sources set-up that could collect data for this indication. NHSE has expressed that new, mandated NHSE-wide data collection is not currently in its plans. Therefore, any RWE for this topic will be provided by the company. In its managed access proposal, the company describes several RWE studies it intends to carry out (see Trial Data tab for more information): 1) Comparative long-term effectiveness studies are to be carried out in the US and Europe, which will provide long-term real-world evidence of patients treated with donanemab compared with a matched placebo cohort 2) A real-world evidence study is planned for 2024 and is anticipated to complete in Q4 2024. The study will generate evidence on resource use in both health and social care provision for patients with MCI due to AD and patients with AD dementia over time, based on integrated UK datasets 3) A real-world evidence study is planned for the period 2024 – 2026, with annual data read-outs describing the patient diagnostic and disease management profile within the UK, inclusive of the use of biomarkers for diagnosis The company also explains: • Lilly are also exploring additional sources of data collection for resolving key areas of uncertainty. Should donanemab receive a recommendation through managed access, the above sources and any further data collection that is initiated would be used to inform the evidence base for the cost-effectiveness analysis in the resubmission to NICE

Data Source		
Relevance to managed access		
Existing, adapted, or new data collection	New	
Prior experience with managed access	Low	
Relevance of existing data items	Low	
If required, ease that new data items can be created / modified	Not applicable	
How quickly could the data collection be implemented	Unclear	
Data quality		
Population coverage	Low	
Data completeness	Low	
Data accuracy		
Data timeliness		
Quality assurance processes		
Data availability lag		
Data sharing / linkage		
New data sharing arrangements required?		
New data linkages required?		
If yes, has the governance of data sharing been established		
Analyses		
How easily could collected data be incorporated into an economic model		

Existing methodology to analyse data		
If no, is there a clear process to develop the statistical analysis plan		
Existing analytical capacity		
Governance		
Lawful basis for data collection		
Privacy notice & data subject rights		
Territory of processing		
Data protection registration		
Security assurance		
Existing relevant ethics/research approvals		
Patient consent		
Funding		
Existing funding		
Additional funding required for MA		
If yes, has additional funding been agreed in principle		
Service evaluation checklist - registry specific questions		
HRA question 2. Does the study protocol demand changing treatment/care/services from accepted standards for any of the patients/service users involved?		
Does data collection through registry require any change from normal treatment or service standards?	Yes	
Are any of the clinical assessments not validated for use or accepted clinical practice	No	
HRA question 3. Is the study designed to produce generalisable or transferable findings?		
Would the data generated for the purpose of managed access be expected to be used to make decisions for a wider patient population than covered by the marketing authorisation / NICE recommendation	No	
Additional considerations for managed access		
Are the clinical assessments and data collection comparable to current clinical practice data collection?	Yes	
Burden		
Additional patient burden	No	
Additional clinical burden	Yes	
Other additional burden	Yes	

Other issues

Explanation

This page details the Managed Access Team's assessment on whether there are any potential barriers to agreeing a managed access agreement and that any potential managed access agreement operates according to the policy framework developed for the Cancer Drugs Fund and Innovative Medicines Fund.

The items included are informed by the relevant policy documentation, expert input from stakeholders including the Health Research Authority, and the Managed Access team's experience with developing, agreeing and operating managed access agreements. Additions or amendments may be made to these considerations as further experience is gained from Managed Access.

The Managed Access Team will justify it decision, but broadly it is a matter of judgement on whether any issues identified, taken as a whole, are likely to lead to a barrier to a Managed Access Agreement being agreed, or operationalised in the NHS. No assessment is made whether a Commercial Access Agreement is likely to be reached between the company and NHS England, which could be a substantive barrier to managed access.

Are there any substantive issues (excluding price) that are a barrier to a MAA	
Overall rating	**Rationale/comments**
Yes - Major	High burden from any new data collection arrangements; implementation would be burdensome in routine commissioning and managed access; restricted implementation would go against IMF principles; complexity of topic would likely delay DCA development.

		Rating	Rationale / comments
Burden	Expected overall additional patient burden from data collection?	High	Data collection within current practice does not exist and therefore there would be additional burden. Collection would need to be in primary and secondary care, which would be complex to implement.
	Expected overall additional system burden from data collection?	High	Data collection within current practice does not exist and therefore there would be additional burden. Collection would need to be in primary and secondary care, which would be complex to implement.
	Do stakeholders consider any additional burden to be acceptable		Would need to check with NHSE in particular
	Would additional burden need to be formally assessed, and any mitigation actions agreed, as part of a recommendation with managed access	Yes	This is unclear

		Rating	Rationale / comments
Patient Safety	Have patient safety concerns been identified during the evaluation?		TBC
	Is there a clear plan to monitor patient safety within a MA?		TBC
	Are additional patient safety monitoring processes required	No	Unlikely to require safety monitoring further than what would be expected in routine commissioning

		Rating	Rationale / comments
Patient access after MAA	Are there are any potential barriers to the agreed exit strategy for managed access, that in the event of negative NICE guidance update people already having treatment may continue at the company's cost		IMF principles say that in the event of a negative recommendation at exit treatment will continue at the company's cost. The large budget impact may affect the company's willingness to enter managed access.
	If yes, have NHS England and the company agreed in principle to the exit strategy		TBC

		Rating	Rationale / comments
Service implementation	Is the technology disruptive to the service	No	Disruption would be the same for routine commissioning and managed access. Therefore, managed access would not subject system to additional burden, as things stand.
	Will implementation subject the NHS to irrecoverable costs?	Yes	Implementation through routine commissioning or managed access would be expensive and resource-intensive.

	Is there an existing service specification which will cover the new treatment?	Unclear	Service for this treatment would be a significant deviation to current care.

		Rating	Rationale / comments
Patient eligibility	Are there specific eligibility criteria proposed to manage clinical uncertainty	Unclear	Will depend on committee decision making. IMF principles dictate that the treatment needs to be made available to the entire eligible population for the indication.
	If yes, are these different to what would be used if the technology had been recommended for routine use?	Not applicable	

		Rating	Rationale / comments
Service evaluation checklist	HRA question 1. Are the participants in your study randomised to different groups?		
	Will the technology be available to the whole recommended population that meet the eligibility criteria?	No	Current discussions suggest implementation will be limited at first.
	HRA question 2. Does the study protocol demand changing treatment/care/services from accepted standards for any of the patients/service users involved?		
	Will the technology be used differently to how it would be if it had been recommended for use?	Unclear	There may be differences in how the drug would be rolled in managed access to routine commissioning but this is unclear.
	Any issues from registry specific questions	No	
	HRA question 3. Is the study designed to produce generalisable or transferable findings?		
	Any issues from registry specific questions	No	
	Additional considerations for managed access		
	Is it likely that this technology would be recommended for routine commissioning disregarding the cost of the technology?	Unclear	Difficult to assess for this indication
	Any issues from registry specific questions	No	No suitable registry identified

		Rating	Rationale / comments
Equality	Are there any equality issues with a recommendation with managed access	Unclear	Restricted implementation could have equality issues

		Rating	Rationale / comments
Timings	Likelihood that a Data Collection Agreement can be agreed within normal FAD development timelines	Unclear	What data could be collected would depend on how the drug is implemented, and if delayed would delay any DCA development