Single Technology Appraisal

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

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

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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 Eisai
   a. Full submission
   b. Submission addendum

2. **Company summary of information for patients (SIP)** from Eisai

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
   g. NHS England

5. **Expert personal perspectives** from:
   a. Dr Richard Perry – clinical expert, nominated by Eisai
   b. Professor Elizabeth Coulthard – clinical expert, nominated by Alzheimer's Research UK
   c. Larry Woelk – patient expert, nominated by Alzheimer's Research UK

   - David Thomas – patient expert, nominated by Alzheimer's Research UK (*see document 4a.*)
   - Ann Jarvis – commissioning expert, nominated by NHS England (*see document 4g.*)

6. **External Assessment Report** prepared by Kleijnen Systematic Reviews
   a. External Assessment report
   b. EAG addendum – additional scenarios
   c. EAG addendum – APOE4 test costs
   d. EAG response to company submission addendum

7. External Assessment Report – factual accuracy check

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

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

Document B

Company evidence submission

December 2023

File name	Version	Contains confidential information	Date
[ID4043]_Lecanemab_Company evidence submission_Document B_7Dec23_[CON] Updated 23Feb24_REDACTED	Final	Yes	4th June 2024

Contents

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Abbreviations

AChEI	Acetylcholinesterase inhibitor
AD	Alzheimer's disease
ADA	Antidrug antibody
ADAS-Cog14	Alzheimer's Disease Assessment Scale-Cognitive subscale 14-item version
ADCOMS	Alzheimer's disease composite score
ADL	Activities of daily living
ADCS MCI-ADL	Alzheimer's Disease Cooperative Study – Activities of Daily Living for Mild Cognitive Impairment
AE	Adverse event
AESI	Adverse event of special interest
ANCOVA	Analysis of covariance
APC	Alzheimer's prognostic covariate
APOE4	Apolipoprotein E4
ARIA	Amyloid-related imaging abnormalities
ARIA-E	Amyloid-related imaging abnormality-oedema/effusion
ARIA-H	Amyloid-related imaging abnormality-microhaemorrhage and haemosiderin deposit
AUC	Area under the plasma concentration-time curve
BACE	β-site amyloid precursor protein cleaving enzyme
BADL	Basic activities of daily living
BMI	Body mass index
BNF	British National Formulary
CDR	Clinical Dementia Rating
CDR-SB	Clinical Dementia Rating – Sum of Boxes
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
COVID-19	Coronavirus disease of 2019
CRF	Case report form
CRO	Contract research organisation
CSF	Cerebrospinal fluid
C-SSRS	Columbia suicide severity rating scale
DES	Discrete event simulation
DMT	Disease modifying therapy
DQoL	Dementia Quality of Life Instrument
Early AD	Mild cognitive impairment due to AD or mild dementia due to AD
ECG	Electrocardiogram
EMA	European Medicines Agency
FAQ	Functional Assessment Questionnaire

FAS	Full Analysis Set
FDA	Food and Drug Administration
GDS	Geriatric Depression Scale
HCP	Healthcare professional
Heter	Heterozygous
Homo	Homozygous
HRQoL	Health-related quality of life
IADL	Instrumental activities of daily living
iADRS	Integrated Alzheimer's disease rating scale
ICER	Incremental cost-effectiveness ratio
IgG1	Immunoglobulin G1
INR	International normalised ratio
IQ	Intelligence quotient
ITT	Intent-to-treat
IV	Intravenous
IxRS	Interactive voice and web response system
Kg	Kilogram
Lec	Lecanemab
LME	Linear mixed effects
LY	Life year
LYG	Life years gained
M	Months
Max	Maximum
MCI	Mild cognitive impairment
MCID	Minimally clinically important difference
MedRA	Medical Dictionary for Regulatory Activities
Mg	Milligram
MHRA	Medicines and Healthcare products Regulatory Agency
MI	Multiple imputations
Mild AD	Mild dementia due to AD
Min	Minimum
MMRM	Mixed effects model with repeated measures
MMSE	Mini mental state examination
MRI	Magnetic resonance imaging
N	Number of patients at each visit
N	Number of patients in treatment group
NC	Not calculated
NFL	Neurofilament light chain
NHS	National Health Service
NIA-AA	National Institute of Aging-Alzheimer's Association

OLE	Open-label extension
PAS	Patient Access Scheme
PASLU	Patient Access Schemes Liaison Unit
PBO	Placebo
PD	Pharmacodynamics
PEI	Paul-Ehrlich-Institut
PET	Positron emission tomography
PK	Pharmacokinetics
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
QALY	Quality-adjusted life year
QoL	Quality of life
QOL-AD	Quality of life in Alzheimer's disease
R	Randomisation
ROI	Region of interest
SAE	Serious adverse event
SAS	Safety Analysis Set
SD	Standard deviation
SE	Standard error
SLR	Systematic literature review
SmPC	Summary of product characteristics
SoC	Standard of care
SOP	Standard operating procedure
SUVR	Standard uptake value ratio
TEAE	Treatment-emergent adverse event
TIA	Transient ischaemic attack
VAS	Visual analogue scale
vMRI	Volumetric magnetic resonance imaging
WMS-IV LMSII	Wechsler Memory Scale IV-Logical Memory (subscale) II
ZBI	Zarit's Burden Interview

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

B.1.1 Decision problem

This submission covers the full expected marketing authorisation for lecanemab, specifically for the treatment of adults with mild cognitive impairment or mild dementia caused by Alzheimer's disease, collectively known as early Alzheimer's disease.

The decision problem is aligned with the NICE final scope as outlined in Table 1 and the NICE reference case.[1,2]

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 mild cognitive impairment (MCI) or mild dementia due to Alzheimer's disease (AD).	In line with scope	N/A
Intervention	Lecanemab plus established clinical management.	In line with scope	N/A

Comparator(s)	Established clinical management without lecanemab, including, but not limited to:
	• For MCI due to AD
	  ○ Non-pharmacological management
	• For mild dementia due to AD
	An acetylcholinesterase (AChE) inhibitor plus non-pharmacological management
		Established clinical management without lecanemab, including, but not limited to:
		• For MCI due to AD
		  ○ Non-pharmacological management
		• For mild Alzheimer's disease-related dementia:
		  ○ An acetylcholinesterase (AChE) inhibitor and/or non-pharmacological management
			Changed from "plus non-pharmacological management" to "and/or non-pharmacological management" to align with the Clarity AD trial and UK guidelines for dementia.[3,4]

Outcomes	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 • Health-related quality of life • Adverse effects of treatment	In line with scope	N/A
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.	In line with scope, with the addition of a scenario analysis considering a broader NHS and PSS perspective including as the costs of unpaid care that might otherwise be provided by the NHS or PSS.	In line with NICE's methods manual for health technology evaluations, costs outside the NHS & PSS perspective, such as unpaid caregiving, that might otherwise be provided by the NHS or PSS may be considered within the NHS and PSS perspective.[5]
Subgroups to be considered	If the evidence allows the following subgroups will be considered: • Apolipoprotein E 4 (*APOE4*) gene carrier status • Mild cognitive impairment due to Alzheimer's disease • Mild dementia due to Alzheimer's disease	Scenario analyses for MCI due to AD and mild dementia due to AD are presented.	N/A

Special considerations, including equity or equality issues	No equality issues have been identified.	In line with scope	N/A

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

B.1.2 Description of the technology being appraised

Table 2 summarises the technology being appraised in this submission. The Summary of Product Characteristics (SmPC) can be found in Appendix C.

Table 2: Technology being appraised

UK approved name and brand name	Lecanemab (brand name to be confirmed following marketing authorisation).
Mechanism of action	AD is a progressive neurodegenerative disease characterised by the accumulation of both amyloid beta (Aβ) plaques and tau tangles in the brain, known as neurofibrillary tangles (NFT). Aβ plaques are composed of Aβ peptides of varying length in particular the 42 amino acid isoform (Aβ1-42).[6] There is a plethora of evidence to indicate that accumulation of aggregation of Aβ plaques is the initial trigger for the series of events that ultimately lead to AD. This is known as the amyloid hypothesis, as presented in Figure 1 and described in Section B.1.3.1.1.[7,8] Prior to Aβ plaque formation, the Aβ peptide evolves through different structures of different solubility and size. Individual Aβ peptides (known as soluble monomers) aggregate together to form aggregates of increasing size (dimers, trimers, oligomers, protofibrils). Protofibrils eventually aggregate together to form the insoluble fibrils which make up Aβ plaques. The accumulation of Aβ plaques, alongside tau tangles, are the main characteristics of AD, described in further detail in Section B.1.3.1.1.[9] Lecanemab is a humanised monoclonal antibody (IgG1) that binds to aggregated amyloid beta (Aβ) peptides, marking them for clearance via the immune system. Lecanemab has the highest binding affinity for soluble toxic Aβ protofibrils, whilst maintaining binding activity to oligomers and insoluble fibrils, as demonstrated in the pre-clinical studies of lecanemab.[10] Targeting the protofibrils for clearance in turn inhibits their toxic properties, but also reduce further downstream Aβ plaque formation. Due to Aβ being the trigger of the amyloid cascade, reducing further Aβ plaque deposition and inhibiting Aβ protofibril toxicity affects the downstream pathology of AD, including Tau pathology. Lecanemab has been shown to also slow down the spread of Tau. During AD, Tau generally spreads in astereotypical neuroanatomical manner known as Braak stages.[11] Lecanemab slows Tau spread in different

	brain areas, with most significance in the medial temporal lobe, an early Braak region which is an early hallmark of disease progression.[12] Deposition and accumulation of Aβ occurs decades before symptoms in AD begin, known as the preclinical stage of AD. Therefore, targeting these Aβ protofibrils in the early stages of AD, and in turn reducing Aβ plaque formation and further downstream pathology, could slow the progression of the disease. If approved, lecanemab will be the only anti-Aβ disease modifying therapy (DMT), available to patients in the UK.[8,13–19]
Marketing authorisation/CE mark status	Lecanemab does not currently have marketing authorisation in the UK as the Medicines and Healthcare products Regulatory Agency (MHRA) procedure is under assessment. The GB National Marketing Authorisation Application submission occurred on 19 May 2023 and provisional decision date (Day 150) is in February 2024, or April 2024 if an additional clock-stop is needed.
Indications and any restriction(s) as described in the SmPC	In the draft SmPC, the indication wording is: '[redacted]'.[20] This is subject to change following the MHRA's final decision.
Method of administration and dosage	The recommended dose of lecanemab is 10 mg/kg. Lecanemab is administered as an intravenous (IV) infusion, over approximately one hour, once every 2 weeks. [redacted].[20]
Additional tests or investigations	The presence of Aβ pathology must be confirmed via an appropriate test prior to initiating treatment.[20] It is anticipated that the test to confirm brain Aβ pathology will be carried out using one of the following: • Cerebrospinal fluid (CSF) biomarker test • Amyloid positron emission tomography (PET) scan

	[redacted] Further details on dosing interruptions for patients with amyloid-related imaging abnormality-oedema/effusion (ARIA-E) and amyloid-related imaging abnormality-microhaemorrhage and haemosiderin deposit (ARIA-H) are provided in Section B.2.3.1.2.
List price and average cost of a course of treatment	The list price has been submitted but is not yet approved by DHSC. The proposed list price of lecanemab is £[redacted] for one vial of 200 mg powder for concentrate for solution for infusion and £[redacted] for one vial of 500 mg powder for concentrate for solution for infusion. The average monthly cost of treatment per the Clarity AD core study is £[redacted] based on the weight distribution of the subset of European patients in the ITT population of Clarity AD.
Patient access scheme (if applicable)	[redacted]

Abbreviations: AD – Alzheimer's disease; CHMP – Committee for Medicinal Products for Human Use; CSF – Cerebrospinal fluid; DHSC Department of Health and Social Care; IgG1 – Immunoglobulin G1; MCI – Mild Cognitive Impairment; SD – Standard deviation; SmPC – Summary of product characteristics

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

Overview of AD, epidemiology, humanistic and economic burden

- Alzheimer's disease is the leading form of dementia and cause of cognitive impairment in individuals aged ≥65 years throughout the world.[21] Prevalence of AD is high and expected to increase consistent with ageing of the general global population.[22,23] Prevalence rises with age and is higher among women than among men.[29,30] AD progresses through several stages; preclinical, MCI, mild dementia, moderate dementia, and severe dementia due to AD (henceforth referred to as mild AD, moderate AD, and severe AD, respectively).[21,26–30]
- Brain amyloid is a defining pathological feature of AD that precedes and predisposes tauopathies, neurodegeneration, and cognitive decline.[28]
- Alzheimer's disease is a cause of premature death, most commonly due to secondary infections often related to severe disease.[31,32]
- As AD progresses, patients require more assistance, beginning to lose independence in basic daily functions at the moderate AD stage.[33] Severe AD is marked by substantial cognitive impairment, the inability to perform basic daily functions, and complete dependence on a carer. Neuropsychiatric symptoms such as apathy, anxiety, mood changes, aggression/agitation, and depression may occur in early AD, and frequently occur in later stages of disease, alongside delusions and hallucinations.[21,30]
- Cognition, activities of daily living (ADLs), social interaction, and psychological factors interact in a complex fashion to affect patient's health-related quality of life (HRQoL).[34,35] As a patient's ability to conduct ADLs diminishes with disease progression, their HRQoL is negatively impacted.[36–39] In more severe stages of disease, difficulty in obtaining accurate self-reported information in this population necessitates assessments from patient proxies, such as family members or caregivers.
- There is a significant burden for caregivers of patients who experience the emotional toll of witnessing their loved one's decline, and the physical demands of providing round-the-clock care can further lead to anxiety and exhaustion.[40]
- The annual social and informal care cost of dementia is currently £22.7 billion in the UK, with over 1.1 million 25 to 49 year-olds out of work due to caring responsibilities related to AD.[41]

Current clinical pathway

- Currently, no treatment guidelines exist for MCI due to AD. Available treatments for AD in the UK clinical pathway (acetylcholinesterase inhibitors and memantine) provide only symptomatic relief. As such, these treatments transiently alleviate cognitive impairment but do not treat the underlying cause of AD nor cure, halt, or delay disease progression, highlighting the unmet need for effective DMTs in AD.

Lecanemab

- Lecanemab, a humanised monoclonal (IgG1) antibody that rapidly clears amyloid plaques and highly toxic protofibrils.
- Lecanemab is expected to be the first DMT for early AD indicated in the UK, subject to MHRA approval.

B.1.3.1 Overview of AD

Alzheimer's disease is a chronic, irreversible neurodegenerative disorder, causing cognitive difficulties including memory loss, confusion, and personality changes. AD is the leading cause of cognitive impairment and dementia worldwide in individuals aged 65 and above.[21] With disease progression, AD patients lose their ability to live independently and become completely dependent on others for their care.[42] This places a substantial burden on individuals affected by the disease, their families, the health and social care system, and UK economy, causing over 1.1 million 25 to 49 year olds to be out of work as a result of caring responsibilities related to AD and an estimated £22.7 billion annual cost on social and informal care.[41]

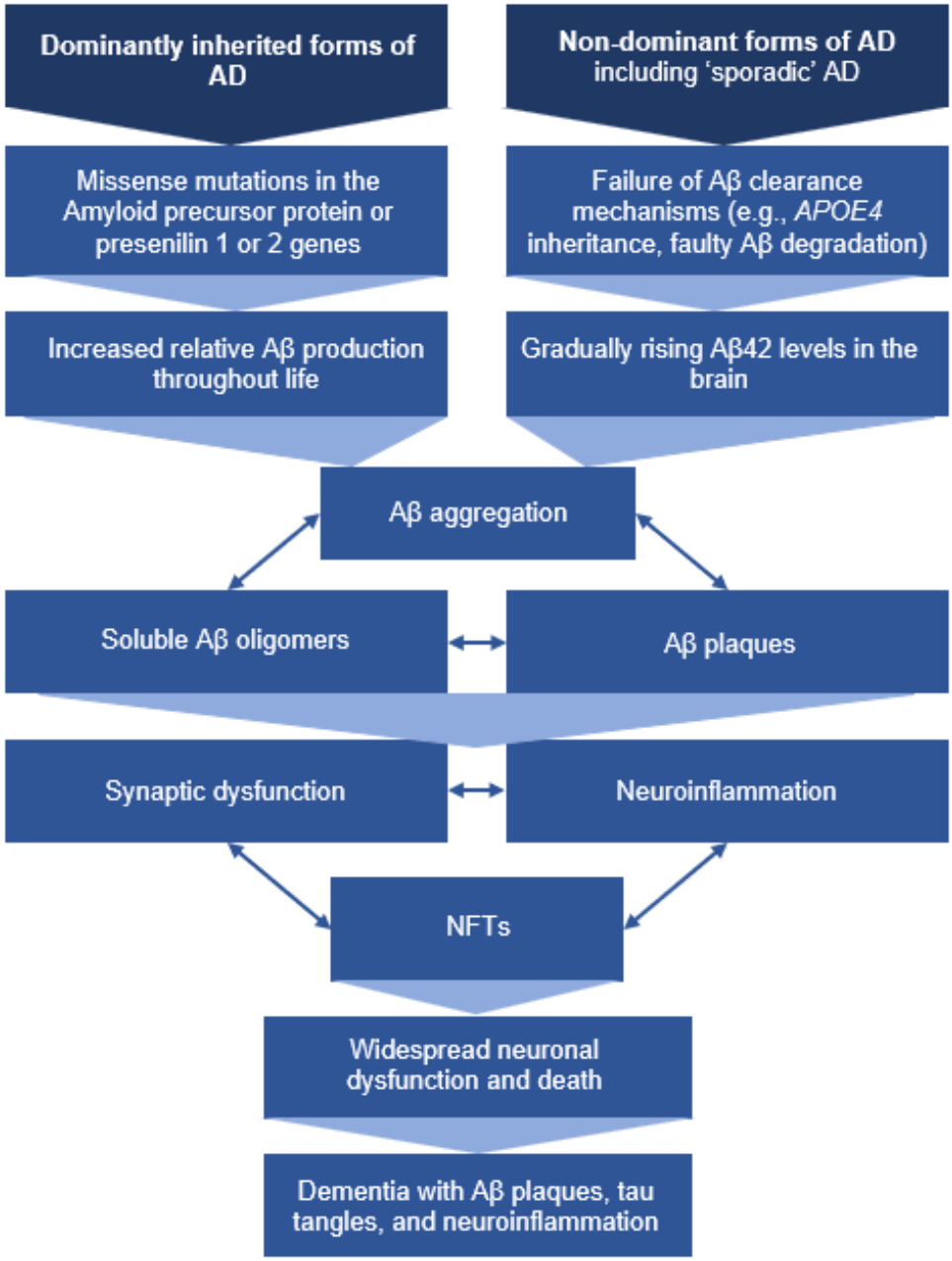
B.1.3.1.1 Pathophysiology

Alzheimer's disease is a neurodegenerative disease characterised by deposition of extracellular Aβ plaques composed of Aβ peptides and intracellular neurofibrillary tangles (NFT) composed of the Tau protein. Aβ plaque deposition occurs first, followed by NFT accumulation, brain atrophy and finally cognitive and functional defects.

Prior to Aβ plaque formation, Aβ proteins evolve through various forms in the brain before forming plaques, including monomers, oligomers, protofibrils, fibrils, and eventually Aβ plaques.[13,43–45]. The buildup of Aβ starts a harmful chain reaction in AD, known as the amyloid cascade (Figure 1), causing inflammation, oxidative stress, and other biological processes that lead to the formation of neurofibrillary tangles (i.e., aggregated tau), synaptic dysfunction, synapse loss, and neurodegeneration.[13–16] Formation of Tau tangles (NFT's) occurs downstream of Aβ deposition and marks disease progression. The spread of NFT's occurs in a predictable and stereotypical manner, described as Braak stages, starting in the medial temporal lobe in the earlier stages of the disease and spreading into the limbic and neocortical regions in the more advanced stages of the disease.[11]

Growing evidence suggests that insoluble forms of Aβ (oligomers and protofibrils) are the most harmful to brain cells; they can directly damage cells, disrupt connections between them, and impair memory processes.[46] Reducing these harmful Aβ forms could therefore provide a means to stop further brain damage.[8,13–19]

Figure 1: The amyloid cascade



Abbreviations: Aβ – amyloid beta; AD – Alzheimer's disease; NFTs – Neurofibrillary tangles.
Source: Selkoe et al (2016)[8], Morris et al (2014)[7]

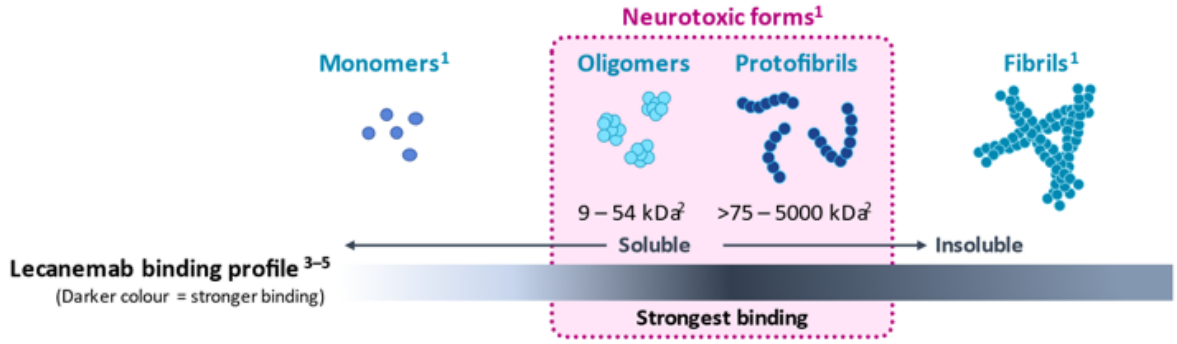
Early-onset (dominantly inherited) AD is associated with familial mutations in presenilin-1 (PSEN1), presenilin-2 (PSEN2), and amyloid precursor protein (APP) genes, as shown in Figure 1. These genetic risk factors are believed to lead to increased generation of Aβ, causing formation of oligomers and eventually leading to the development of Aβ plaques. Late onset (non-dominant or 'sporadic') AD is the most common form of AD, and typically occurs after the age of 60.[47] This form of AD is associated with the *APOE* gene, with the biggest genetic risk factor for late-onset AD being the presence of at least one *APOE4* allele. *APOE4* is thought to lead to reduced Aβ clearance, contributing to the accumulation of Aβ and thus the

development of Aβ plaques. As such, these processes are thought to contribute to the pathogenesis of Alzheimer's disease.[7]

The amyloid hypothesis suggests that aggregation of Aβ is the initial trigger for the series of events that ultimately lead to AD. Therefore, targeting Aβ plaques could inhibit the 'trigger' leading to the pathology seen in AD.

Prior to Aβ plaque formation, the Aβ peptide evolves through different structures of different solubility and size (Figure 2). Individual Aβ peptides (known as soluble monomers) form aggregates of increasing size (dimers, trimers, oligomers, and protofibrils). Protofibrils eventually aggregate together to form the insoluble fibrils which make up Aβ plaques. As such, reducing the formation of protofibrils results in reduction of downstream Aβ plaque formation.

Figure 2: Amyloid plaque formation and lecanemab binding profile



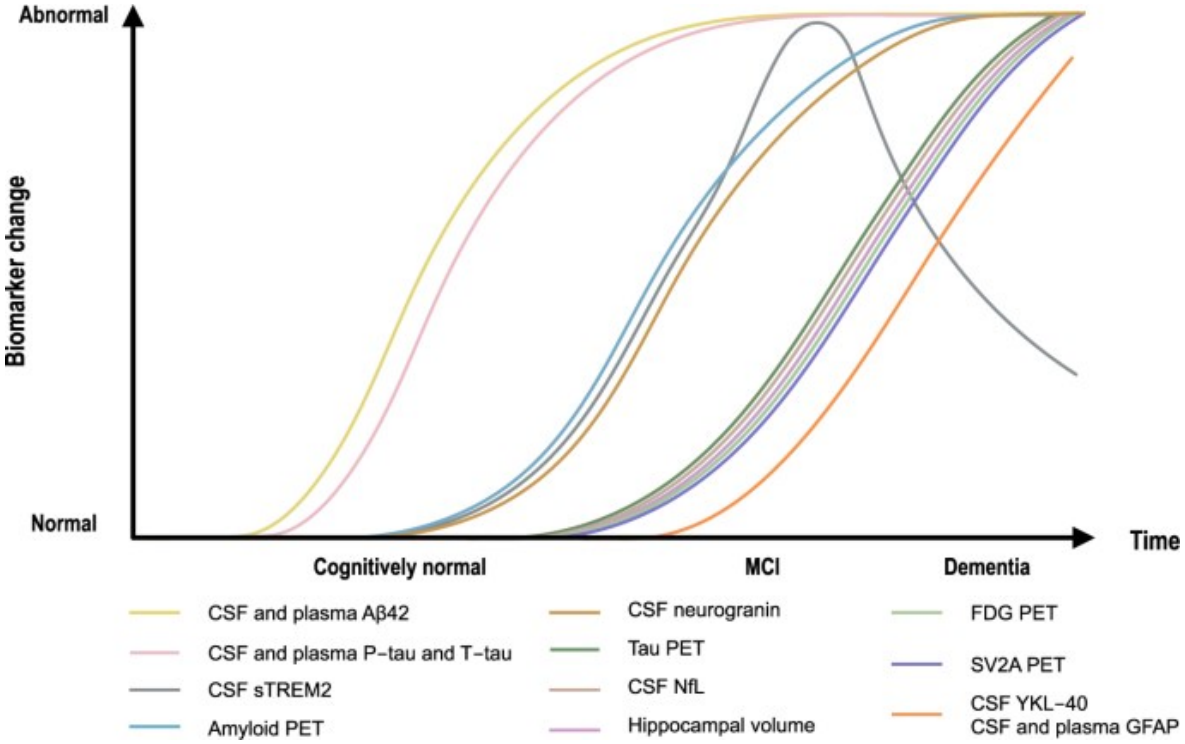
Abbreviations: kDa – Kilodalton
Source: Irizarry (2022)[50]

There is growing evidence to suggest that soluble Aβ protofibrils and oligomers are the most neurotoxic of all Aβ species. Evidence suggests Aβ protofibrils are directly toxic to neurons and induce cell death. These peptides also disturb healthy synapse activity, which is essential for a functioning nervous system, and impair important neuronal functions, such as memory formation.[13–19]

AD progresses slowly over time, with deposition and accumulation of amyloid beta occurring decades before symptoms of AD begin, known as the preclinical stage of AD. The pathological cascade of AD showing the change in amyloid beta and other key AD biomarkers over time is presented in Figure 3. Following initial accumulation of CSF and plasma Aβ42, increases in CSF and plasma p-Tau and t-Tau occur as a neuronal response to the amyloid changes. Amyloid PET subsequently increases to 'positive' levels (Section B.2.6.2.2), followed closely by increases in CSF neurogranin, indicating synaptic dysfunction. When Tau PET reaches positive levels, numerous neurodegeneration and synaptic dysfunction biomarkers change in parallel, including reduction in hippocampal volume and increases in CSF neurofilament light (NfL), fluorodeoxyglucose (FDG) PET, and SV2A PET. Finally, increases in astrocytic biomarkers (YKL-40 and glial fibrillary acidic protein [GFAP]) are believed to occur relatively late in the disease process.[54]

In many cases, by the time AD is diagnosed, significant and irreversible brain damage has already occurred.[55] This underscores the critical importance of early diagnosis and the need for timely intervention.

Figure 3: Model of AD pathological cascade



Abbreviations: Aβ – Amyloid beta; AD – Alzheimer's disease; CSF – Cerebrospinal fluid; FDG – Fluorodeoxyglucose; GFAP – Glial fibrillary acidic protein; MCI – Mild cognitive impairment; NfL – Neurofilament light; PET – Positron emission tomography; sTREM2 – soluble triggering receptor expressed on myeloid cells 2; SV2A – Synaptic vesicle protein 2A
Source: Zetterberg et al., 2020[54]

B.1.3.2 Clinical staging

Alzheimer's disease progresses through several stages: preclinical, MCI, mild dementia, moderate dementia, and severe dementia (henceforth referred to as mild AD, moderate AD, and severe AD, respectively).[21,26–30] Preclinical AD represents the presence of AD pathological hallmarks including Aβ deposition and tau tangle formation, but an absence of clinical symptoms.[28,29] Thereafter, symptoms of typical AD begin in MCI with subtle changes in cognition an impairment in short-term memory. MCI develops into mild short-term memory loss, word finding difficulties, other cognitive deficits, with initial impairment of functioning as patients progress to mild AD.

MCI due to AD and mild AD are collectively referred to as early AD, the target population for lecanemab and the scope of this submission. Figure 4 summarises the staging of AD, including early AD, in the context of the disease pathway and the associated impact on cognition and function.

Figure 4: Stages of AD

	Asymptomatic	First clinical symptoms	Increasing clinical impact	Serious functional and cognitive impairment	
Cognitive impact	No signs of cognitive decline[1,2]	Slight changes in cognitive function and temporary lapses in short-term memory e.g., challenges recalling recent names or events[1]	Individuals or their family members might observe memory lapses, such as difficulties in recalling the right word or name, and instances of misplacing or losing important items.[4]	Increased confusion and behavioural symptoms e.g., forgetfulness of personal history, feelings of depression leading to withdrawal[4]	Restricted awareness of surroundings
Functional impact	No functional impairment[1,2]	Subtle yet noticeable decline in functional ability e.g., difficulty judging the time or sequence of events needed to complete a task, or visual perception[2,3]	Possible difficulties with IADLs e.g., managing finances and medication, food preparation, housekeeping, and communication with others[5,6]	Struggles with ADLs e.g., personal hygiene, grooming, and dressing[1,4]	Diminished physical capabilities involving challenges in speech, swallowing, transferring or ambulating, coupled with elevated susceptibility to infections[1,4]
Overall functioning	Patients are active and independent	No noticeable limitations on social or occupational functioning[1,2]	Patients still able to function independently[4]	Requires an increased level of caregiving[4]	Requires full-time care – patients are completely dependent[4]

Source: 1: Alzheimer's Association 2018[56]; 2: Jack 2018[28]; 3: Alzheimer's Association 2020[57]; 4: Alzheimer's Association 2020[58]; 5: Marshall 2015[59]; 6: Kernisan 2019[60]
Abbreviations: AD – Alzheimer's disease; ADL – Activities of daily living; IADL – Instrumental activities of daily living; MCI – Mild cognitive impairment

AD is diagnosed using a variety of approaches and tools through a multidisciplinary assessment of the patient's history, physical examination and psychological testing (see Section B.1.3.6 for more details).[61,62] Early diagnosis of AD, when a patient is still functionally independent, can allow management and treatment initiation in milder stages of disease, with the potential to prolong the patient's independence and maintaining a higher quality of life than that expected in more severe stages of disease.[63] However, diagnosis often occurs once a patient has already reached mild AD or later stages.[64]

There are several scales for measuring AD severity, primarily focussing on cognition, function, or a combination of both. The Clinical Dementia Rating (CDR) – Sum of Boxes (CDR-SB), ADAS-Cog14, Global CDR, The Mini-Mental State Examination (MMSE) and the Alzheimer's Disease Composite Score (ADCOMS) measure severity according to cognition and function.

CDR-SB is a validated outcome measure used in clinical trials of AD to capture cognition and function by interviewing patients and their care partners.[65] It measures six domains that patients and caregivers identify as important: memory, orientation, judgement and problem solving, community affairs, home and hobbies, and personal care. Scores for each domain range from 0 to 3, with higher scores indicating greater impairment. Total scores range from 0 to 18.[66]

The Global CDR score, which can also be used to determine dementia stage, is rated from 0 to 3, with higher scores indicating greater impairment. Table 3 presents how CDR-SB and Global CDR ratings map to AD severity. Table 9 presents a more detailed summary of the scales used as endpoints in the core Clarity AD study.

Table 3: CDR-SB and Global CDR dementia staging scores

Clinical disease stage	CDR-SB	Global CDR
MCI due to AD	0.5-4.0	0.5
Mild dementia due to AD	4.5-9.0	1.0
Moderate dementia due to AD	9.5-15.5	2.0
Severe dementia due to AD	16.0-18.0	3.0

Source: O'Bryant et al.[66]
Abbreviations: AD – Alzheimer's disease; MCI – Mild cognitive impairment; CDR – Clinical Dementia Rating; CDR-SB – Clinical Dementia Rating Sum of Boxes

Patients with MCI experience insidious progression in severity until their higher-level daily function is impacted as they reach mild dementia. Elements of cognition that decline as the disease progresses include attention and concentration, language, constructional praxis, visuospatial ability, executive function, fluency, and verbal intelligence quotient (IQ).[67,68]

As progression continues, patients require more assistance with daily functions. When patients reach moderate dementia, symptoms become more pronounced and patients lose independence in basic activities of daily living.[33,58] Patients experience memory loss, delusions, confusion, and difficulty expressing thoughts, contributing to personality and behavioural changes such as frustration, suspiciousness, and anger. Patients with moderate AD also experience difficulty controlling their bladder and bowels, and show an increased tendency to wander and become lost, thus requiring a greater level of care.[58]

Finally, severe AD is marked by severe cognitive impairment and an inability to perform basic daily functions, leading to complete dependence on a carer. Neuropsychiatric symptoms such as anxiety, mood changes, aggression/agitation worsen as the disease progresses causing substantial personality changes, and eventually patients experience delusions/hallucinations in severe stages of the disease.[21,30,58] Patients with severe AD struggle to converse and to communicate their pain, and eventually lose the ability to control their movement, thus requiring extensive daily care.[58]

Patients with severe AD become vulnerable to infections, particularly pneumonia.[58] As a result, AD is a cause of premature death, most commonly due to such secondary infections, often related to severe disease.[31,32] As a result, mortality increases with AD severity. In a Danish study of mortality in dementia patients spanning 14 years, the hazard ratio for death compared with individuals without dementia increased from 1.82 for patients with MCI due to AD, up to 9.52 for patients with severe AD.[69] In the UK, 11.4% of total deaths in 2022 were attributed to

dementia and AD.[70] Life expectancy in individuals diagnosed with AD can be as little as 3 to 10 years post-diagnosis for those in their 60s and early 70s, compared to 18 to 27 years for the general population aged 60-70.[71,72]

B.1.3.3 Epidemiology

The prevalence of AD dementia is high and expected to rise over time due to a global ageing population, with AD affecting 3% to 4% of adults in their late working or retirement years.[22–25,73–76] As of June 2023, 465,516 people in the UK have a recorded diagnosis of dementia, 97% of which are over the age of 65.[77] AD accounts for almost half of those diagnosed with dementia (43.4%, 203,541 people).[77] AD is a continuum progressing through stages from MCI due to AD and mild, moderate, and severe AD (Section B.1.3.1). The target population for lecanemab is patients with MCI due to AD or mild AD, collectively referred to as early AD, with confirmed amyloid pathology.

B.1.3.3.1 Prevalence of MCI due to AD

It is estimated that between 5% and 20% of adults over 65 years of age in the UK have MCI, totalling approximately 165,000-660,000 people.[57,78,79] People with MCI are at greater risk of developing dementia and AD in particular. In research studies carried out in memory clinics, 10-15% of people who had MCI with gradual memory loss went on to develop dementia.[57]

Certain groups are disproportionately affected by MCI due to dementia, namely the older population. A recent meta-analysis found that the incidence of clinically-diagnosed MCI rises with age, increasing from 22.5 cases per 1000 person-years among people aged 75 to 79 years to 60.1 cases per 1000 person-years among people aged ≥85 years.[80]

B.1.3.3.2 Prevalence of mild AD

It is estimated that 48% of prevalent cases of AD are classified as mild, indicating that of 203,541 people in the UK with AD, approximately 97,700 have mild AD.[81]

B.1.3.3.3 Disproportionate prevalence in AD

People from Black, Asian, and minority ethnic communities living in the UK may be at higher risk of developing dementia due to increased exposure to dementia risk factors, resulting in 20% higher incidence of dementia in Black adults compared to the UK average.[82]

Women are also disproportionately impacted by dementia, making up nearly two thirds (65%) of dementia cases in the UK as well as almost two thirds of unpaid carers of those with dementia.[83] In 2020, dementia killed almost double the number of women than men in the UK (46,000 versus 24,000).[84]

B.1.3.3.4 Mortality

In England, the number of deaths attributed to dementia in individuals aged 75 years and older has doubled in a decade, rising from 40,253 cases in 2007 to 87,199 cases in 2017.[85] Dementia was the leading cause of death in 2022 and has been the leading cause of death for women since 2011. In England and Wales, dementia accounted for 11.4% of all deaths in 2022.[86]

B.1.3.4 Humanistic burden

AD has a substantial negative effect on HRQoL for both patients and their carers. Many people living with AD require around-the-clock assistance with daily personal care, lose physical abilities, such as walking, sitting, and eventually swallowing, and have difficulty communicating, with symptoms considerably worsening in later stages of disease, as described in B.1.3.2.[58] Caring for a family member or friend with AD can have a substantial burden on caregivers HRQoL through poor family functioning, difficult patient behaviour and concerns about the patient's illness, in addition to time spent caregiving, impacting on carers mental and physical wellbeing.[87]

B.1.3.4.1 Patient burden

For patients living with AD, cognition, ADLs, social interaction, and psychological factors interact in a complex fashion to affect HRQoL.[34,35] The ability to perform ADLs is an important component of QoL.[34,35] ADLs are classified into instrumental (IADL) and basic (BADL). IADLs include more complex activities enabling independence such as managing finances and medications, food preparation, housekeeping, laundry, and communication with others.[88] Loss of IADLs may become increasingly apparent early in the disease course prior to formal diagnosis, and are therefore useful indicators for the onset of cognitive decline.[89]

Loss of BADLs tends to occur in later, more severe stages of AD with patients losing the ability to communicate, experiencing changes in physical capabilities including walking, sitting and swallowing, in addition to severe memory loss.[58]

Inability to conduct ADLs has a negative relationship on patients' HRQoL, thus HRQoL decreases with disease severity, as ability to conduct IADLs and then BADLs diminishes.[36–39] A study of French patients with mild to moderate AD found patients who could still perform ADLs such as using the telephone had significantly higher scores (p=0.05) on the self-esteem domain of the Dementia Quality of Life Instrument (DQoL) than patients who could not.[90] Similarly, a UK-based study found that deteriorating total ADL performance had a negative impact on QoL for patients with moderate dementia.[91]

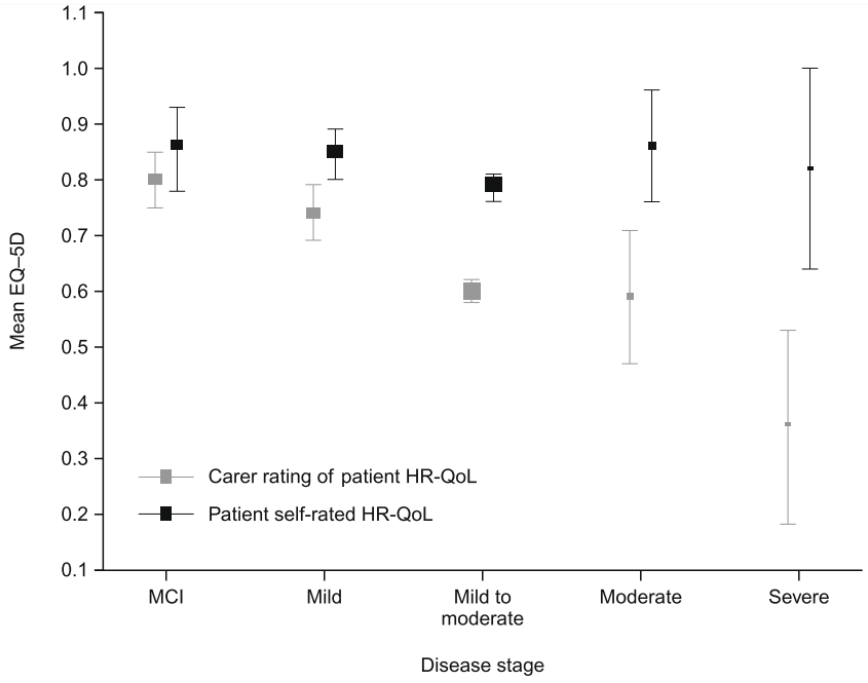
A 2020 cross-sectional study exploring the impact of institutionalisation on patients' HRQoL found that patients experience a disutility of -0.16 when they are institutionalised, which occurs more frequently in later stages of disease (Table 4), as measured by a patient by proxy reported EQ-5D score.[37] Institutionalisation impacts patients' ability to think and act independently, and cognitive decline has

been shown to be significantly faster for patients once institutionalised.[92,93] Further, a study of UK, German, and French patients using a weighted EQ-5D total health status index score, with a range from 0 (dead) to 1 (perfect health), found a statistically significant ($p<0.001$) fall in patient HRQoL from 0.71 at mild disease, to 0.51 at severe stage of disease.[38]

Measuring HRQoL of AD patients is complicated due to the many factors that can affect HRQoL and the difficulty in obtaining accurate self-reported information in this population, particularly in more severe disease stages. This difficulty arises from cognitive impairments and non-cognitive symptoms like depression and psychosis. In many cases, investigators must rely on assessments from patient proxies, such as family members or caregivers, rather than obtaining self-reported data directly from the patients themselves.[94,95] The variation in EQ-5D by patient and carer reported values, according to disease severity is seen in Figure 5. The findings indicate that there is little variation in the utility values for MCI patients, however the gap between self- and proxy-reported utilities grows with severity of disease.

A study of UK patients in care homes found large differences between proxy-reported and self-reported QoL, with patients rating their QoL higher than both relatives and formal carers, highlighting the difficulty of recording accurate self-reported QoL for patients.[96] Furthermore, family caregiver's estimates of functional impairment have been shown to be accurate when compared with objective function, indicating that proxy measures are useful for measuring the impact of AD on patients.[97]

Figure 5: HRQoL measured using the EQ-5D



Abbreviations: HRQoL – Health-related quality of life; MCI – Mild cognitive impairment
Source: Landeiro et al. 2020[95]

B.1.3.4.2 Caregiver burden

AD also has a substantial impact on HRQoL for carers. At the time of diagnosis, carers report feeling worried, sad and uncertain.[98] A 2018 research trial conducted by Alzheimer's Society found that 90% of caregivers for people with dementia experience feelings of stress or anxiety several times a week.[99] Furthermore, 83% of carers have felt lonely or isolated because of their caring responsibilities.[41] Carers told Alzheimer's Society of how they struggled with exhaustion due to countless sleepless nights, lack of socialising, and neglecting their own health. In a case study by Alzheimer's Research UK, one carer described the significant "psychological and physical" strain of looking after his mother, who became "increasingly violent", especially when providing intimate personal care.[100] In the UK, 1.3 billion hours of unpaid care are provided by family and other caregivers each year.[101] Another UK study revealed that 87% of people with dementia receive help from family in their day-to-day life, indicating the scale of burden on patients' loved ones.[102] Carer HRQoL is also negatively impact by disease severity with carer disutility more than doubling between the mild and severe stages of AD.[36] These studies indicate the substantial burden faced by caregivers, in terms of emotional strain, time spent caring and subsequently the impact on their ability to work. The societal burden due to young caregivers being out of work is explored in further detail in Section B.1.3.5.2.

B.1.3.5 Economic burden

The economic burden of AD in the UK is significant and is substantially broader than the impact on the health and social care systems. The economic cost to the UK of caring for people with dementia is expected to grow from £25 billion in 2021 to £47 billion in 2050, including direct medical costs (outpatient, hospitalisation, out of pocket), direct nonmedical costs (transport, accommodation, meals, formal care) and indirect costs (informal care, intangible costs).[41] If the current trajectory continues and no DMTs are made available, dementia is anticipated to be the UK's most expensive health condition by 2030, if no DMTs are made available.[103]

Social and informal care costs account for the vast majority of the costs of dementia care in the UK, with 52% of total dementia costs (£12.9 billion) attributable to social care costs and 39% of the total (£9.7 billion) attributable to informal care costs.[104] Healthcare costs account for just 7% (£1.7 billion) of the total costs in the UK.[103] As the severity of AD increases, the costs associated with AD become higher, largely due to the greater need for care and support for individuals at advanced stages of the disease.[105–108]

B.1.3.5.1 Direct costs

Prior to the onset of AD, patients with MCI due to AD incur excess costs versus matched controls without AD due to an increase in hospitalisations, longer hospital stays, more physician visits, and a greater need for home health services.[109–112]

Once patients progress to AD, direct medical costs continue to rise.[105–108] A multinational survey covering the UK, France, Italy, Germany, Spain, the US, and Canada (n=6,143) found that resource use rose with increasing dementia severity (Table 4) for the majority of resource elements assessed (primary care visits, other provider visits, institutionalisation, and hospitalisations).[113] Professional caregiver hours required per week dramatically rose once patients progressed to moderate and severe AD.

Table 4: Healthcare resource use in the UK utilisation by severity of cognitive impairment (n=815), Khandker et al. 2020[113]

Resource	Very mild n=120	Mild n=294	Moderate n=340	Severe n=61
PCP consultations within the last 12 months, mean (SD)	1.7 (1.8)	2.8 (3.5)	2.6 (2.8)	3.4 (3.9)
Specialist consultations within the last 12 months, mean (SD)	1.7 (1.8)	2.0 (1.9)	2.2 (2.1)	2.1 (2.2)
Other HCP consultations within the last 12 months, mean (SD)	0.7 (1.8)	1.0 (3.5)	1.3 (3.1)	1.4 (2.7)
All-cause consultations within the last 12 months, mean (SD)	0.1 (0.3)	0.3 (0.7)	0.5 (0.9)	0.8 (0.9)
Dementia-related hospitalisations within the last 12 months, mean (SD)	0.0 (0.1)	0.1 (0.3)	0.1 (0.5)	0.1 (0.4)
Professional caregiver hours required per week, mean (SD)	4.0 (22.4)	6.6 (25.5)	26.6 (51.7)	76.1 (75.3)
Number currently institutionalised (n, %)	2 (1.7)	12 (4.1)	58 (17.1)	37 (60.7)

Abbreviations: HCP – Healthcare professional; PCP – Primary care physician.
Specialists: neurologists, geriatricians, psychiatrists, psycho-geriatricians, neuropsychiatrists, and specialists in memory clinics. Other HCPs: community psychiatrists, physiotherapists, social workers, and other HCPs. Data shown are for patients with evaluable data for each characteristic.
Source: Khandker et al. 2020[113]

B.1.3.5.2 Societal burden

The majority of costs related to dementia care do not fall within healthcare budgets; instead, they often extend beyond traditional healthcare expenditures. Dementia care encompasses various domains, including long-term care, social services, caregiver support, and other non-medical expenses that can significantly impact families and society as a whole. At present, £1.7 billion is spent by the NHS on dementia versus £22.7 billion spent by social and informal care.[114] These costs manifest in the form of unpaid care provided by family members and the direct expenses associated with private social care services. This underscores the significant financial and caregiving burden placed on those affected by dementia and their loved ones. In 2019, the total cost of social care for AD was estimated to be £15.7 billion in the UK, while unpaid care costs for AD in the UK totalled £13.9

billion.[104] Projections indicate that by 2040, the costs of social care and unpaid care will reach £45.4 billion and £35.7 billion, respectively, primarily driven by the growing prevalence of AD and the rise in per-patient costs.[115]

A large proportion of individuals living with dementia rely on daily assistance from family members or caregivers, with 87% of people with dementia receiving help from family in their day-to-day life, and only 14% receiving help from a paid carer.[102] According to a survey, approximately 40% of those caring for individuals with dementia provide constant, "round-the-clock" care.[99] This caregiving role can be physically and emotionally challenging, often leaving caregivers with limited opportunities to take breaks or time off from their caregiving responsibilities.[99]

The responsibilities associated with caring for individuals with dementia can exert a substantial financial impact on caregivers and their households. One of the reasons for this is the need for caregivers to leave their jobs or reduce their working hours to provide care. Statistics in 2017 indicated that 17% of caregivers end up completely giving up their employment, while 25% have to reduce their working hours due to their caregiving duties.[102] In 2023, it is predicted that 1.1 million 25-49 year olds are out of work because of caring responsibilities.[114] Approximately one in every three caregivers are in part- or full-time employment (28.3%).[116] These adjustments can result in a loss of income and productivity for caregivers and their families.[102] Additionally, a 2019 report by the Centre for Economics and Business Research projected that by 2040, approximately 53,400 individuals will exit the workforce prematurely due to dementia. This represents a significant loss of valuable skills and expertise, estimated to be worth over £2 billion to English businesses.[117] Furthermore, caregivers cover many of the costs of caring out of their own pockets. This impacts retired caregivers in particular, who live on fixed incomes and therefore may be less able than employed caregivers to absorb these costs or seek relief through respite care or daycare programs, thereby amplifying the effects on their HRQoL.[118]

Potential cost drivers in patients with AD include dementia severity, patient dependence level, cognitive and/or functional decline, institutionalisation, and agitation.[105,119,120] As patients progress into the severe stages of dementia due to AD, they are more likely to require full-time care, which contributes to increased total caregiver time and higher informal care costs.[120,121] A multicentre, cross-sectional, observational study conducted at 18 sites in England (the DADE study) used a multivariate model to demonstrate that as patient dependence increased, caregiver burden increased. Multiple regressions using a generalised linear model showed a one-point increase in the Dependence Scale was associated with 2.15-point increase in the Zarit Burden Interview (ZBI) score, a tool developed to measure subjective burden among caregivers of adults with dementia on a scale of 0 (low burden) to 88 (high burden). This finding suggests that as patients advance through the stages of AD, the burden on their caregivers increases at a disproportionately higher rate, underscoring the critical importance of slowing disease progression thus

alleviating burden on caregivers. The model also suggested that if the patient was not in a nursing home/residential care facility, the ZBI score was expected to increase by 19 points, indicating greater caregiver burden.[122] Additional burden to the caregiver results in increased time spent caring, thereby increasing financial burden.

In a 2022 meta-analysis study of the cost of dementia in Europe, mean annual care costs per patient in the UK increased according to AD severity, with the highest total costs in those with severe dementia (€61,958 [95% CI: 10,603, 113,312]), as compared with moderate (€34,223 [[95% CI: 25,263–43,183]) and mild dementia (€19,909 [[95% CI: 14,977, 24,841]).[123]

These data highlight the economic need for a DMT in early AD which can prevent or delay the progression of AD, thereby reducing the total societal cost burden of this disease.

B.1.3.6 Clinical pathway in early AD

B.1.3.6.1 Diagnosis

Diagnosing AD does not rely on one single test, making the current patient journey to diagnosis complex. General practitioners, along with specialists such as neuropsychologists, old-age psychiatrists, neurologists, neuroradiologists, and geriatricians use a variety of approaches and tools to help make a diagnosis through a multidisciplinary assessment (as presented in Figure 6).[61]

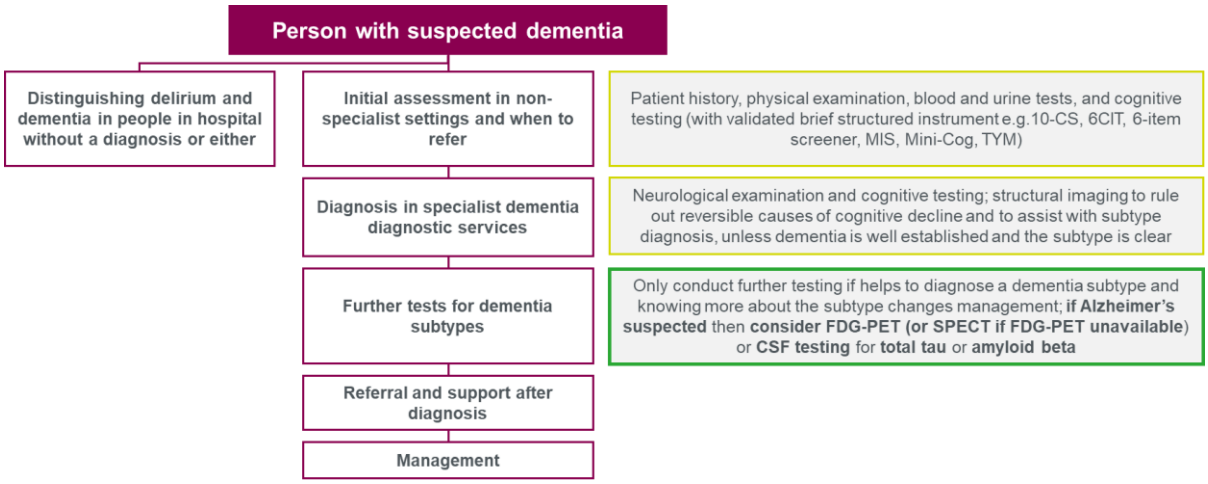
An initial assessment is conducted in a non-specialist primary care setting, during which the patient's history is taken, including basic measurement of cognitive, behavioural, and psychological symptoms, as well as the impact the symptoms have on their daily life. If possible, history is taken from both the patient and someone who knows them well, such as a family member. These tests cannot diagnose dementia; however, they may confirm memory difficulties which require further investigation.

A physical examination is conducted following initial assessment if dementia is still suspected, alongside blood and urine tests and cognitive testing. Cognitive testing involves the use of a validated cognitive instrument such as the 10-point cognitive screener, the 6-item cognitive impairment test, the 6-item screener, the Memory Impairment Screen (MIS), the Mini-Cog, or the Test Your Memory (TYM).

Patients are referred to a specialist dementia diagnostic service if AD is suspected following physical examination, such as a memory clinic or community old age psychiatry service, at which a test of verbal episodic memory is conducted. Psychological testing is then conducted to determine if the patient's cognitive impairment is caused by dementia and the correct subtype diagnosis.[61,62] Healthcare specialists may consider neuropsychological testing if it is unclear whether the

person has cognitive impairment, whether the cognitive impairment is caused by dementia, or what the correct diagnosis of subtype is. These diagnoses follow established criteria, such as the NIA-AA criteria for AD or the Movement disorders Society criteria for Parkinson's disease dementia.[124,125] If diagnosis is still uncertain and AD is suspected, diagnostic testing such as FDG (fluorodeoxyglucose)-PET, perfusion SPECT (single-photon emission CT), or CSF biomarker testing can be undertaken.

Figure 6: Dementia assessment and diagnosis



Abbreviations: 10-CS – 10-point cognitive screener; 6CIT – Six Item Cognitive Impairment Test; CSF – Cerebrospinal fluid; FDG-PET – Fluorodeoxyglucose-positron emission tomography; MIS – Memory Impairment Screen; SPECT – Single photon emission computed tomography; TYM – Test Your Memory
Source: NICE guideline NG97[62]

Irrespective of the availability of a DMT for early AD, it is beneficial for both patients and their families to confirm diagnosis of AD, offering a plausible explanation for the patients' symptoms. Additionally, this determination provides families and medical practitioners with the time needed to plan the most effective approach for handling the disease and accessing appropriate services.[63,126] A timely diagnosis enables patients to actively engage in making decisions concerning legal, financial, and future care matters before the onset of more severe cognitive decline. It also potentially extends the period during which patients can continue residing in their own homes and minimises the impact of the condition on their quality of life and that of their families.[63,126] However, the 2021 National Audit of Dementia – Memory Assessment Services Spotlight found there to be marked variations between services with regard to key assessments, diagnostic investigations and post diagnostic support.[127]

B.1.3.6.2 Treatments

There are currently no approved pharmacological or non-pharmacological treatments nor published treatment guidelines for MCI due to AD in the UK. As such, wide variation exists in treatment practice for these patients.[128] For patients with dementia due to AD, management primarily follows the NICE guideline for assessment and

management of dementia (NG97), which recommends pharmacological and non-pharmacological treatments (Table 5).[4] A more detailed, recently published interpretation of NG97 is shown in Figure 24, Appendix O1.2. At present, pharmacological treatment is comprised of three acetylcholinesterase inhibitors (AChEIs) and one N-methyl-D-aspartate (NMDA) receptor antagonist. NICE recommends either donepezil, galantamine or rivastigmine for mild to moderate AD. Memantine is recommended in combination with an AChEI for moderate to severe AD. For patients who are intolerant or have a contraindication to AChEIs, memantine can be taken as a monotherapy.

Table 5: Symptomatic treatments for AD (NICE guideline NG97)[4]

<table>
<tr><th>MCI due to AD</th><th>Mild dementia due to AD</th><th>Moderate dementia due to AD</th><th>Severe dementia due to AD</th></tr>
<tr><td rowspan="2">No guideline available</td><td rowspan="2">AChE inhibitors:
• Donepezil
• Galantamine
• Rivastigmine</td><td>AChE inhibitors:
• Donepezil
• Galantamine
• Rivastigmine

For patients who are unable to take AChE inhibitors:
• Memantine</td><td>NMDA receptor antagonists:
• Memantine</td></tr>
<tr><td colspan="2">For patients with an established AD diagnosis:
• AChE inhibitor + memantine</td></tr>
</table>

Source: NICE Guideline NG97[4]
Abbreviations: AChEI – Acetyl cholinesterase inhibitor; AD – Alzheimer's disease; MCI – Mild cognitive impairment; NMDA – N-methyl-D-aspartate

It is important to note that these treatments provide only symptomatic relief, thereby temporarily alleviating cognitive impairment, but do not treat the underlying cause of AD, nor cure or halt progression of the disease.[129,130]

Recommended non-pharmacological management for mild to moderate dementia includes social support, increasing assistance with day-to-day activities, information and education, carer support groups, community dementia teams, home nursing and personal care, community services, befriending services, day centres, and in later stages of disease, respite care and care homes.[4] Additionally, group stimulation therapy, group reminiscence therapy, cognitive rehabilitation therapy and occupational therapy are used in order to promote cognition, independence and wellbeing.[62]

B.1.3.7 Unmet need

There is a severe unmet need for an intervention that delays AD progression, preserving patients' independence for longer, thus alleviating patient and carer burden by slowing the decline in HRQoL and easing financial burden on patients and their carers. AD is a condition characterised by a slow and gradual progression. The

accumulation of toxic oligomers, protofibrils, and Aβ plaques and hyperphosphorylation of tau start to occur up to 20 years before the first noticeable clinical symptoms appear. In many cases, by the time a diagnosis of AD is made, significant and irreversible brain damage has already occurred. This underscores the critical importance of early diagnosis and intervention to potentially slow down or mitigate the impact of the disease.[131]

AD has a profound impact on patients and their relatives and caregivers. Caregivers of AD patients face an extreme challenge due to the complexity, unpredictability and progression of the disease, with financial burden, difficult patient behaviour, and volume of caregiving hours found to worsen caregiver QoL.[132]

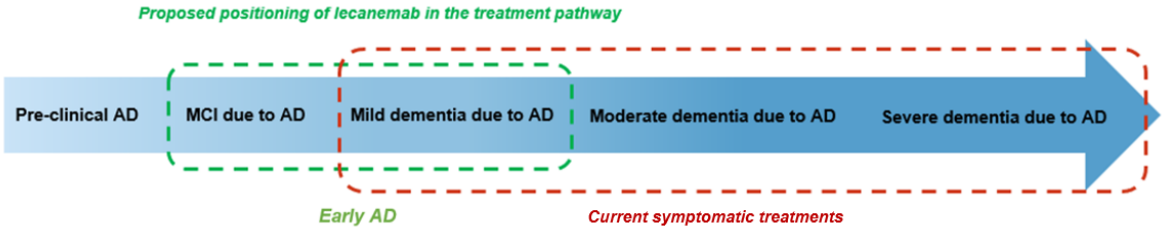
Currently available therapies for AD provide only temporary symptomatic relief, and do not treat the underlying cause of AD nor cure or halt the progression of the disease.[129,130] This unmet need is heightened for patients with MCI due to AD for whom no pharmacological treatments are currently recommended, who have the potential to remain in less severe stages of disease for longer. Delaying disease progression allows patients greater function by increasing capacity for ADLs, prolongs time spent with higher QoL comparable to later stages of disease, delays increased burden on their caregivers, and delays the risk of further irreversible decline.[133] Dementia is the only major cause of death without a treatment to prevent, slow or stop disease progression.[85]

Considering the substantial impact of AD and the symptomatic nature of current therapies, there exists a significant unmet need for an effective treatment focused on diminishing the clinical deterioration by targeting the root causes of AD. Lecanemab therefore has the potential to alter the outlook for individuals with MCI due to AD or mild AD and should ideally be administered as early as possible following diagnosis in order to slow the progression of disease and delay decline in both functional capabilities and cognitive function.[134]

B.1.3.8 Anticipated positioning of lecanemab in the treatment pathway

Lecanemab is anticipated to be offered to patients with early AD (MCI due to AD or mild AD, Figure 7), subject to regulatory approval and a positive reimbursement decision. This unique positioning would provide the first DMT for patients with early AD, including for patients with MCI for whom no treatments are currently recommended.

Figure 7: Proposed positioning of lecanemab in the clinical pathway of care



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

Currently, there is no established treatment course for individuals with MCI due to AD. A new diagnostic pathway for AD would also be required to identify patients most likely to benefit from a DMT and ensure early diagnosis to mitigate the impacts of the disease prior to the onset of irreversible cognitive decline.

Symptomatic treatments will continue to be offered to patients with mild AD as required, therefore it is not anticipated that the approval of lecanemab would impact patient's access to these therapies and can be used in combination where required.

B.1.4 Equality considerations

There are no known equality issues relating to the use of lecanemab in patients with early AD.

B.2 Clinical effectiveness

Evidence for this submission comes from the pivotal Phase III, multicentre, randomised, placebo-controlled, double-blind, parallel-group, Clarity AD study of lecanemab vs placebo in patients with early AD)[3]

- Primary analyses results are for the 18-month core study period.[135] Clarity AD included 1,795 patients and presents a robust evidence base for lecanemab.[135]
- Clarity AD included eight UK sites and the Clarity AD baseline characteristics were deemed generalisable to UK clinical practice by UK clinical experts.[136,137]
- A systematic literature review (SLR) was conducted to identify evidence in this setting.

Clarity AD met the primary endpoint of change from baseline in CDR-SB at 18 months between lecanemab and placebo[135]

- Lecanemab demonstrated a highly statistically significant slowing in cognitive decline compared with placebo at 18 months, with an adjusted mean treatment difference of -0.451, 27.1% less decline in change from baseline in CDR-SB (p=0.00005). Highly statistically significant differences were observed as early as six months and across all subsequent time points (all p<0.01).
- Slope analysis indicates increasing differentiation over time between lecanemab and placebo, with a 29.3% slowing of slope on lecanemab annually compared to placebo (p=0.00001). This suggests preservation of CDR-SB by approximately 5.3 months relative to placebo at 18 months.

Lecanemab demonstrated a highly statistically significant reduction compared to placebo in all key secondary endpoints, including measures of cognitive and functional decline and activities of daily living[135]

- Lecanemab significantly reduced amyloid plaque burden (as measured by amyloid PET using Centiloids) with an adjusted mean change of -55.5 and 3.6 Centiloids from baseline for lecanemab and placebo, respectively, at 18 months (adjusted mean treatment difference: -59.1; p<0.00001).
- Lecanemab slowed cognitive decline by 25.8% compared to placebo at 18 months on the Alzheimer's Disease Assessment Scale-Cognitive subscale 14-item version (ADAS-Cog14) (p=0.00065).
- Lecanemab slowed cognitive and functional decline by 23.5% compared to placebo at 18 months on ADCOMS (p=0.00002).
- Lecanemab resulted in 36.6% less decline in the Alzheimer's Disease Cooperative Study – Activities of Daily Living for Mild Cognitive Impairment (ADCS MCI-ADL) from baseline compared to placebo at 18 months (p<0.00001).
- Across all key secondary endpoints, the changes from baseline compared to placebo increased over time.

Lecanemab showed a statistically significant difference compared to placebo in proportion of patients converting to amyloid negative[135]

- 60.4% of lecanemab patients converted to amyloid negativity (<30 CL) at 18 months, compared to only 0.6% of placebo patients.
- There is a relationship between reduction in amyloid PET and clinical decline on CDR-SB (Pearson correlation coefficient=0.82, p=0.0463).
- Mediation analyses conducted to explore the relationship between the effect of lecanemab on CDR-SB showed 80% of the effect on CDR-SB can be explained by reduction in amyloid PET (Centiloids).[138]

Lecanemab reduced progression to the next stage of AD by 31% based on the global CDR score[135]**, meaning patients remain in more independent stages of the disease for longer**

- In the lecanemab group, [redacted]% of patients experienced a worsening of global CDR at 18 months compared to [redacted]% in the placebo group. The associated hazard ratio of disease progression was 0.69 (95% CI [0.572, 0.833], *p*=0.00011).

Lecanemab showed statistically significant differences compared with placebo at 18 months using patient- and carer-reported quality of life instruments[135]

- There was a highly statistically significant difference between placebo and lecanemab on change from baseline in EQ-5D-5L VAS at 18 months in the Patient's Survey, QOL-AD total score in the Patient's Survey and Partner as a Proxy Survey, and ZBI of Study Partner Total Score (49.1%, *p*=0.00383; 55.6%, *p*=0.00231; 22.9%, *p*=0.02558; 38.4%, *p*=0.00002, respectively).

Lecanemab has a well characterised safety profile demonstrated through consistent incidence of treatment-emergent adverse events (TEAEs) between arms and low death rates

- Overall incidence of TEAEs were similar between lecanemab (88.9%) and placebo (81.9%) and few patients discontinued due to AEs (lecanemab: 7.7%; placebo: 3.2%). The differences in AEs leading to discontinuation are due to AEs of special interest for monoclonal antibodies against Aβ (infusion-related reactions, ARIA).
- Serious adverse events occurred in 11% of placebo and 14% of lecanemab treated patients. The known adverse events of special interest for amyloid lowering monoclonal antibodies accounted for the imbalance relative to placebo in SAEs: The rates of SAE due to infusion related reactions was 1.2%. The rates of SAE due to ARIA-E was 0.8% and due to ARIA-H was 0.6%. Infrequently, ARIA can be serious and life-threatening.
- The rate of radiographically identified ARIA-E was 12.6% for lecanemab and 1.7% placebo. ARIA-E incidence with lecanemab was mostly asymptomatic (lecanemab: 77.9%, placebo: 100.0%), occurred mostly in the first three months of treatment (lecanemab: 70.8% vs placebo: 33.3%), and was mostly radiographically mild or moderate (lecanemab: 91.1% vs placebo: 100.0%). The rate of symptomatic ARIA-E was 2.8% overall with lecanemab.
- The higher rate of ARIA-H with lecanemab (17.3%) versus placebo (9.0%) was driven by ARIA-H occurring concurrently with ARIA-E, which typically occurred within the first three months of treatment. Isolated ARIA-H was similar between lecanemab (8.9%) and placebo (7.8%), with low rates of clinically symptomatic ARIA-H (lecanemab 1.4%; placebo 0.2%); and isolated ARIA-H events occurred infrequently and at a steady rate over 18 months of treatment.
- Death rates during the core study were similar between lecanemab (0.7%) and placebo (0.8%), and no deaths were treatment-related or occurred due to ARIA.

Lecanemab showed an improvement over placebo for pathophysiological biomarkers of amyloid, Tau and neurodegeneration at 18 months.

- In Clarity AD, the baseline level in the lecanemab group was 77.9 Centiloids, and at 18 months, the level was X X X X, a X X X X Centiloid decrease. Lecanemab also showed improvement in other key AD biomarkers (Appendix O1.6).

Lecanemab showed a statistically significant benefit across all measures of cognition, function, and activities of daily living, alongside an acceptable safety profile. In conclusion, lecanemab may be considered an innovative treatment option for patients with early AD and is expected to be the first AD DMT indicated in the UK, subject to MHRA approval.

B.2.1 Identification and selection of relevant studies

A systematic literature review (SLR) was conducted in August 2023 to identify clinical evidence for adult patients with early AD. Full details of the process and methods used to identify the clinical evidence relevant to the technology being appraised are presented in Appendix D.

In addition to the primary population of interest outlined above, evidence for patients with MCI due to unknown reasons was included to ensure that relevant studies related to the decision-making process were included, recognising that MCI due to AD is a relatively recently defined patient population, and a substantial portion of the literature pertains to individuals with MCI without a specific known cause.

The SLR scope included individuals of all racial, ethnic, and gender backgrounds, consistent with the NICE scope. Studies that included mixed populations, such as those with mild dementia due to AD or vascular dementia, were considered if they provided specific information about the populations of interest. These studies were categorised as part of the 'primary literature review'.

The primary search identified 16 randomised control trials (RCTs). The interventions identified in the RCTs included pharmacological interventions (lecanemab and symptomatic treatments) and/or non-pharmacological interventions. The pharmacological (lecanemab, donepezil, and galantamine) and non-pharmacological (cognitive stimulation therapy, reminiscence therapy, cognitive rehabilitation, and occupational therapy) interventions included in the primary search are aligned with the interventions in the NICE dementia guideline (NG97).

The 16 identified RCTs comprise studies across differing disease stages: MCI due to AD (n=3), both mild dementia to AD and MCI due due to AD (n=2), mild dementia due to AD and MCI (reasons unknown) (n=3), and mild dementia due to AD (n=8). Pharmacological treatments included lecanemab (n=2), donepezil (n=2), galantamine (n=4), AChEI + cognitive training (n=1), whilst the remaining RCTs investigated non-pharmacological interventions (n=7).

B.2.2 List of relevant clinical effectiveness evidence

B.2.2.1 Lecanemab

Clarity AD is the pivotal Phase III study supporting the marketing authorisation of lecanemab for patients with early AD. The study demonstrated the ability of lecanemab to safely reduce brain amyloid levels and slow decline across every clinical measure of cognition and function explored with high statistical significance compared to placebo.[3]

Lecanemab dosing in Clarity AD (10 mg/kg biweekly) was based on the Phase II dose-range finding trial (Study 201), which showed a consistent reduction in ADCOMS, CDR-SB, ADAS-Cog14, amyloid PET, and additional CSF biomarkers for

both lecanemab 10 mg/kg monthly and 10 mg/kg biweekly. The 10 mg/kg biweekly dose was identified as the most efficacious dose regimen based on clinical effect on ADCOMS, amyloid lowering, and acceptable risk of ARIA. Together these findings support the targeting of protofibrils in the process of pathophysiological amyloid generation to slow progression in AD.

Table 1 summarises the evidence sources for lecanemab and their use in this submission.

Table 6: Clinical effectiveness evidence for lecanemab – Clarity AD and Study 201

Study	Clarity AD (BAN2401-G000-301) (NCT03887455)	Study 201 (BAN2401-G000-201) (NCT01767311)
Study design	Phase III, multicentre, randomised, placebo-controlled, double-blind, parallel-group, 18-month clinical trial	Phase II, multicentre, randomised, placebo-controlled, double-blind, parallel-group, 18-month clinical trial
Population	Adult patients with early AD	Adult patients with early AD
Intervention(s)	Lecanemab 10 mg/kg biweekly administered as IV infusion	Lecanemab administered as IV infusion via one of the following dosing schedules (in addition to symptomatic treatment): 2.5, 5, or 10 mg/kg bi-weekly or 5 or 10 mg/kg monthly
Comparator(s)	Placebo: biweekly administered as IV infusion (in addition to symptomatic treatment)	Placebo: biweekly administered as IV infusion (in addition to symptomatic treatment)
Indicate if study supports application for marketing authorisation	Yes	Yes
Indicate if study used in the economic model	Yes	No
Rationale if study not used in model	N/A	Study 201 was not used in the economic model as Clarity AD provides direct evidence for the comparison of interest. Study 201 had a different primary endpoint (ADCOMS) to Clarity AD (CDR-SB) and was not powered to detect differences between lecanemab and placebo in CDR-SB score. Only 161 patients in Study 201 were treated with 10 mg/kg biweekly lecanemab, of which only 87 (54.0%) completed study treatment. In contrast, 898 patients were treated with 10 mg/kg biweekly lecanemab in Clarity AD and 729 patients completed the core study.

Reported outcomes specified in the decision problem	Outcomes in bold are incorporated in the model base case and outcomes in italic are included as scenarios: • Cognitive and functional impairment; **CDR-SB,** *Global CDR*, ADCOMS • Cognitive impairment; ADAS-Cog14 • Functional impairment; ADCS-ADL-MCI • Non-cognitive symptoms (e.g., behavioural symptoms): C-SSRS • Biomarker; *Amyloid PET using Centiloids* • **Mortality** • **Adverse effects of treatment** • Patient and carer HRQoL; **EQ-5D-5L (patient-reported, partner as a proxy, study partner),** QOL-AD (Quality of life in Alzheimer's disease) (patient-reported, partner as a proxy), ZBI (study partner only)	• Cognitive and functional impairment; ADCOMS, CDR-SB • Cognitive impairment; ADAS-Cog14 • Biomarker; Amyloid PET SUVR • Mortality • Adverse effects of treatment
All other reported outcomes	• Amyloid PET standardised uptake value ratio (SUVR) • Modified iADRS • Tau PET SUVR • CSF biomarkers (neurogranin [CSF only], NFL, Aβ[1-42], Aβ[1-40], plasma Aβ42/40 ratio, t-tau, and p-tau [including, but not limited to p-tau181) • Volumetric magnetic resonance imaging (vMRI)	• CSF biomarkers • Mini mental state examination (MMSE) • Functional Assessment Questionnaire (FAQ) • Amyloid PET SUVR and visual read • vMRI

Abbreviations: AD – Alzheimer's disease; ADAS-Cog14 – Alzheimer's Disease Assessment Scale-Cognitive subscale; ADCOMS - Alzheimer's disease composite score; ADCS MCI-ADL – Alzheimer's Disease Cooperative Study – Activities of Daily Living for Mild Cognitive Impairment; CDR – Clinical Dementia Rating; CDR-SB – Clinical Dementia Rating – Sum of Boxes; CSF – Cerebrospinal fluid; iARDS – Integrated Alzheimer's disease rating scale; IV – Intravenous; MCI – Mild cognitive impairment; NFL – neurofilament; PET – Positron emission tomography; SUVR – Standard uptake value ratio; QOL-AD – Quality of life in Alzheimer's disease; ZBI – Zarit's Burden Interview.

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

This section describes the methodology of Clarity AD. Study 201 is not summarised here for the reasons described in Section B.2.8.

B.2.3.1 Summary of trial methodology

Clarity AD is a randomised, double-blind, parallel-group, placebo-controlled, multicentre clinical trial to evaluate the safety and efficacy of lecanemab in patients with early AD with confirmed amyloid pathology indicated by positive amyloid load.

Clarity AD was conducted across 14 countries including eight sites in the UK (study design shown in Figure 8)[3] and consisted of:

- A completed pre-randomisation phase (screening period and baseline period, up to 150 days)
- A completed 18-month core study (randomisation phase)
- An ongoing open-label extension (OLE) phase (up to a maximum of 48 months in the clinic, see Section B.2.11 for further detail)

Clinical evaluations in the pre-randomisation phase were organised into five tiers. Tiers 1, 2, and 3 assessments were performed during the screening period, and Tiers 4 and 5 during the baseline period. All assessments and procedures in each tier were completed, and eligibility confirmed, before any assessments or procedures from the next tier commenced. See Table 7 for an overview of the clinical evaluations in the five screening and baseline tiers in Clarity AD. Patients deemed eligible at all tiers entered the core study.

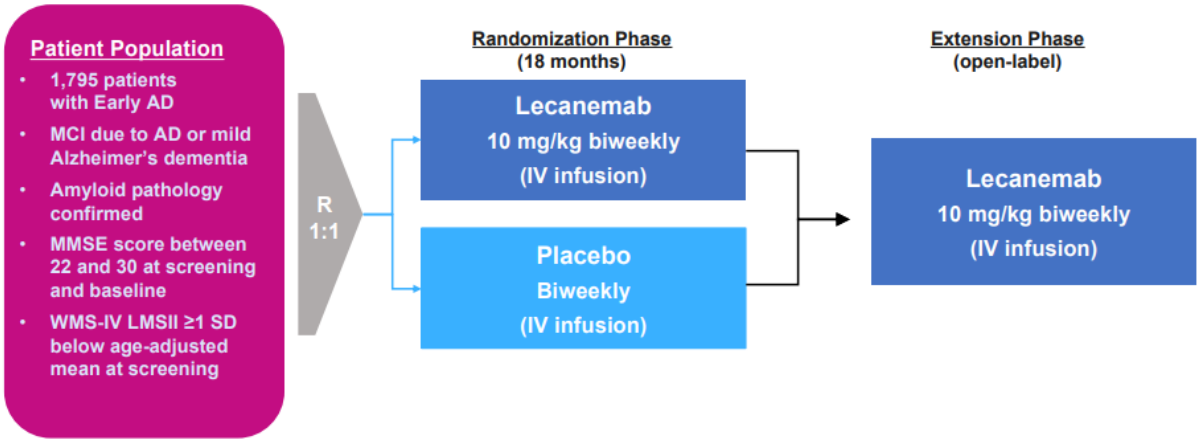
Key protocol amendments were made in response to the COVID-19 pandemic which occurred during the conduct of the study (27 March 2019 to 25 August 2022). Amendments that may have affected patients participating in the study are detailed in Appendix M.

The Safety Analysis Set (SAS) comprised all allocated patients who received at least one dose of study drug. A total of 1,795 patients were included in the SAS and randomised to receive either lecanemab 10 mg/kg biweekly (898 patients), or placebo (897 patients). Both arms continued to receive symptomatic treatment for AD if they were on a stable dose at least 12 weeks prior to baseline. Patients received biweekly IV infusions of lecanemab 10 mg/kg with most patients receiving a concomitant non-AD medication, (lecanemab 99.0%; placebo: 98.7%) and 57.2% and 57.9% of lecanemab and placebo patients receiving a concomitant AD symptomatic medication, respectively (see Table 59, Appendix O for list of concomitant AD medications; list of non-AD concomitant medications too large to include). See Figure 9 for a full breakdown of patient flow in Clarity AD.

Any patient who completed 18 months treatment in the core study (Visit 42 [Week 79]) had the option to continue into the OLE if inclusion and exclusion criteria were met. All patients in the OLE receive open-label lecanemab 10 mg/kg biweekly for up to 48 months (4 years), until the drug is commercially available in the country where the patient resides, or until the benefit-to-risk assessment from treatment with lecanemab is no longer considered favourable, whichever comes first. Of the 729 lecanemab and 757 placebo patients that completed the Clarity AD core study, 671 lecanemab and 714 placebo patients entered the OLE; whilst 58 lecanemab and 43 placebo patients did not enter the OLE upon completion of the core study. Of those who completed the core study, 43 lecanemab patients and 60 placebo patients has progressed to moderate or severe AD, therefore did not meet the eligibility criteria for inclusion in the OLE.

A summary of the methodology of Clarity AD is shown in Table 8.

Figure 8: Clarity AD study design[50]



Abbreviations: AD – Alzheimer's disease; IV – intravenous; MCI – Mild cognitive impairment; MMSE – Mini mental state examination; R – Randomisation; SD – Standard deviation; WMS-IV LMSII – Wechsler Memory Scale IV-Logical Memory (subscale) II

The 'Randomization phase' in this graphic represents the core study of Clarity AD.

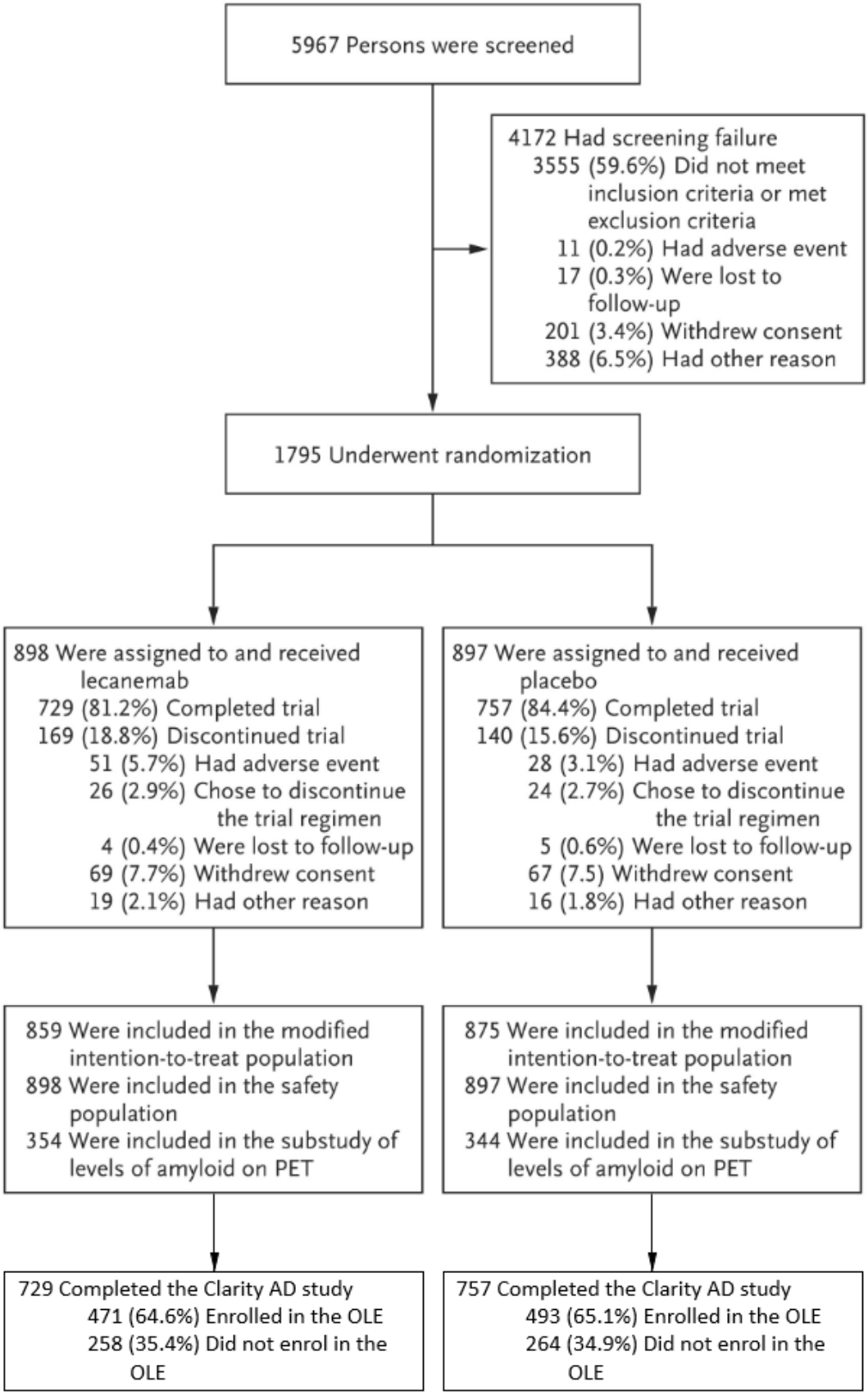
Table 7: Clarity AD screening and baseline tiers

Tier	Procedures carried out
Screening tiers	
Tier 1	• Informed consent • GDS • MMSE, CDR, and WMS-IV LMSI & II
Tier 2	• Physical exam • Vital signs, height, and weight • ECG and labs • C-SSRS • Blood and urine samples collected for clinical laboratory tests and APOE4 carrier assessment
Tier 3	• MRI (safety and volumetric)
Baseline tiers	

Tier 4	• Physical exam, vital signs, and labs • MMSE, CDR, ADAS-Cog14 • EQ-5D-5L, QOL-AD, ADCS MCI-ADL, ZBI • C-SSRS
Tier 5 (for eligibility and baseline for longitudinal substudy)	• Amyloid PET • CSF sampling • Tau PET

Abbreviations: AD – Alzheimer's disease; ADAS-Cog14 – Alzheimer's Disease Assessment Scale-Cognitive subscale; ADCS MCI-ADL – Alzheimer's Disease Cooperative Study – Activities of Daily Living for Mild Cognitive Impairment; *APOE4* – apolipoprotein E4; CDR – Clinical Dementia Rating; CSF – cerebrospinal fluid; C-SSRS – Columbia suicide severity rating scale; ECG – electrocardiogram; GDS – Global Deterioration Scale; MMSE – Mini mental state examination; MRI – magnetic resonance imaging; PET – positron emission tomography; QOL-AD – Quality of life in Alzheimer's disease; WMS-IV LMSI & II – Wechsler Memory Scale IV-Logical Memory (subscale) I & II; ZBI – Zarit's Burden Interview.

Figure 9: Patient flow in Clarity AD



Abbreviations: OLE – open-label extension; PET – positron emission tomography.

Table 8: Clarity AD methodology

Study	Clarity AD (NCT03887455)
Study design and objective	To evaluate the efficacy of lecanemab in participants with early AD by determining the superiority of lecanemab compared with placebo on the change from baseline in the CDR-SB at 18 months of treatment in the core study, with sample size calculations driven by Study 201. Based on data from Study 201, an estimated standard deviation of the change from baseline CDR-SB at 18 months in placebo was 2.031 and an estimated treatment difference was 0.373 in all patients. Therefore, assuming an estimated 20% dropout rate at 18 months in Clarity AD, a total sample size of 1,566 patients had 90% power to detect the treatment difference (see Section B.2.4.2 for full detail on how the sample size was calculated). Lecanemab 10 mg/kg biweekly was identified as the most efficacious dose regimen based on ADCOMS in the dose-finding Study 201 and therefore was used in Clarity AD. This study also evaluated the long-term safety and tolerability of lecanemab in participants with early AD in the OLE and whether the long-term benefits of lecanemab at the end of the core study were maintained over the OLE.
Study location	235 sites in: North America (112), Europe (including Australia) (55), Asia-Pacific (47), and China (21) Of the 55 sites in Europe, eight sites were in UK.
Method of randomisation	Patients were assigned to treatments, (allocated 1:1; lecanemab:placebo), based on a computer-generated randomisation scheme that was reviewed and approved by an independent statistician. Patients were stratified according to clinical subgroup; presence or absence of ongoing approved AD treatment (e.g., AChEIs, memantine, or both); *APOE4* status (i.e., *APOE4* carrier or noncarrier); and geographical region.
Eligibility criteria for participants	Diagnosis of early AD dementia, defined by: • Meeting the NIA-AA core clinical criteria for MCI due to AD–intermediate likelihood, or for probable AD dementia, respectively[139], and • Having a global CDR score of 0.5 (for MCI due to AD) or 0.5-1 (for mild AD dementia), and • Having a CDR Memory Box score of 0.5 or greater at screening and baseline **Key inclusion criteria** • Objective impairment in episodic memory as indicated by at least one standard deviation below age adjusted mean in the Wechsler Memory Scale IV Logical Memory (subscale) II (WMS-IV LMII)[140] • Male and female patients 50 to 90 years, inclusive

	• MMSE score ≥22 & ≤30 at screening and baseline • Positive biomarker for brain amyloid pathology • Body mass index (BMI) greater than 17 and less than 35 at screening • If patients were receiving an approved AD treatment, such as AChEIs, memantine, or both, they had to have been on a stable dose for at least 12 weeks prior to baseline • Have an identified study partner, defined as a person able to support the patient for the duration of the study and who spends at least eight hours per week with the patient • Provided written informed consent • Willing and able to comply with all aspects of the protocol **Key exclusion criteria** • Any neurological condition that could be contributing to cognitive impairment above and beyond that caused by the patient's AD. • History of transient ischaemic attacks (TIAs), stroke, or seizures within 12 months of screening. • Any psychiatric diagnosis or symptoms, (e.g., hallucinations, major depression, or delusions) that could interfere with study procedures in the patient. • GDS score greater than or equal to eight at screening. • Contraindications to MRI scanning, including cardiac pacemaker/defibrillator, ferromagnetic metal implants (e.g., in skull and cardiac devices other than those approved as safe for use in MRI scanners). • Evidence of other clinically significant lesions on brain MRI at screening that could indicate a dementia diagnosis other than AD. • Other significant pathological findings on brain MRI at screening, including but not limited to: more than four microhaemorrhages (defined as 10 mm or less at the greatest diameter); a single macrohaemorrhage greater than 10 mm at greatest diameter; an area of superficial siderosis; evidence of vasogenic oedema; evidence of cerebral contusion, encephalomalacia, aneurysms, vascular malformations, or infective lesions; evidence of multiple lacunar infarcts or stroke involving a major vascular territory, severe small vessel, or white matter disease; space occupying lesions; or brain tumours. • Hypersensitivity to lecanemab or any of the excipients, or to any monoclonal antibody treatment. • Any immunological disease which was not adequately controlled, or which required treatment with immunoglobulins, systemic monoclonal antibodies (or derivatives of monoclonal antibodies), systemic immunosuppressants, or plasmapheresis during the study.

	• Patients with a bleeding disorder that was not under adequate control (including a platelet count <50,000 or international normalised ratio [INR] >1.5 for patients who were not on anticoagulant treatment, e.g., warfarin). Patients who were on anticoagulant therapy had to have their anticoagulant status optimised and be on a stable dose for 4 weeks before screening. Patients who were on anticoagulant therapy were not eligible to participate in CSF assessments. • Any other medical conditions (e.g., cardiac, respiratory, gastrointestinal, renal disease) which were not stably and adequately controlled, or which in the opinion of the investigator could affect the patient's safety or interfere with the study assessments. • Participation in a clinical study involving any therapeutic monoclonal antibody, protein derived from a monoclonal antibody, immunoglobulin therapy, or vaccine within six months before screening unless it could be documented that the patient had been randomised to placebo. • Participation in a clinical study involving any anti-amyloid therapies (including any monoclonal antibody therapies and any β-site amyloid precursor protein cleaving enzyme [BACE] inhibitor therapies) unless it could be documented that the patient only had received placebo. • Patients who had any known prior exposure to lecanemab. • Patients who had been dosed in a clinical study involving any new chemical entities for AD within six months prior to screening unless it could be documented that the patient had been in a placebo treatment arm. • Severe visual or hearing impairment that would have prevented the patient from performing psychometric tests accurately.
Duration of study	Core study: 41 months (27 Mar 2019 to 25 Aug 2022)
Trial drugs	Lecanemab, randomised/completed: 898/729 Placebo, randomised/completed: 897/757
Primary outcomes (explanation of endpoints available in Section B.2.3.1.1 Trial outcomes**)**	Change from baseline in the CDR-SB at 18 months. A detailed explanation of CDR-SB is given in Section B.2.3.1.1 below.
Secondary/tertiary outcomes (explanation of endpoints available in	Key secondary outcomes included: • Change from baseline in amyloid PET using Centiloids at 18 months for brain amyloid levels • Change from baseline in ADAS-Cog14 at 18 months

Section B.2.3.1.1 Trial outcomes**)**	• Change from baseline in ADCOMS at 18 months • Change from baseline in ADCS MCI-ADL at 18 months Other secondary outcomes included: • Incidence of AEs and change in vital signs, electrocardiograms (ECGs), laboratory safety tests, suicidality assessments, and MRI safety parameters • Population pharmacokinetic (PK) parameters of lecanemab in serum, including but not limited, to area under the plasma concentration-time curve (AUC) and average concentration (Cav) Exploratory outcomes included: • Change from baseline in modified iADRS at 18 months • Rate of change over time (mean slope) based on CDR-SB score over 18 months • Time to worsening of global CDR score by 18 months, e.g., the worsening of global CDR score was defined as an increase from baseline by at least 0.5 points on the global CDR scale on two consecutive scheduled visits at which global CDR is undertaken • Correlation of PK exposure with blood and CSF biomarkers, safety parameters, and efficacy (i.e., clinical changes, including CDR-SB, ADAS-Cog14, ADCOMS, ADCS MCI-ADL, and modified iADRS) • Change from baseline in EQ-5D-5L, QOL-AD, and ZBI at 18 months • Describe the characteristics, comorbidities, treatments, associated costs for patients with early Alzheimer's disease, and study partner burden at baseline, before study enrolment, during study participation (including core study and OLE), and after study completion (US only) Results have been reported for the primary and key secondary outcomes, safety and quality of life outcomes, and the key outcome used in the economic analysis, change from baseline in CDR-SB. A detailed explanation of each endpoint is included in Section B.2.3.1.1 below.
HRQoL outcomes	HRQoL was measured using the EQ-5D-5L and QOL-AD at baseline and at every 6-monthly visit. The patients' study partners filled out the EQ-5D-5L and QOL-AD on each patient's behalf, in addition to their own EQ-5D-5L, in order to confirm the validity of the answers provided by the patient. As a result, a set of three EQ-5D-5Ls (patient ['Patient's Survey'], study partner ['Partner's Survey'], and patient-by-proxy for patient ['Partner as a Proxy']), two QOL-ADs (patient and study partner), and one ADCS MCI-ADL (patient) was collected at each visit. Study partner burden was measured every six months using the ZBI to assess the stresses experienced by study partners.

Safety assessments performed	Safety was assessed by monitoring and recording all AEs, monitoring of haematology, blood chemistry and urinalysis, measurement of vital signs, ECGs, and the performance of physical examinations during the treatment period as specified in the Schedule of Assessments. Additional safety assessments specific to this study included brain MRI and the C-SSRS.

Abbreviations: AChEI – acetylcholinesterase inhibitor; AD – Alzheimer's disease; ADAS-Cog14 – Alzheimer's Disease Assessment Scale-Cognitive subscale; ADCOMS – Alzheimer's disease composite score; AE – adverse event; ADCS MCI-ADL – Alzheimer's Disease Cooperative Study – Activities of Daily Living for Mild Cognitive Impairment; *APOE4* – apolipoprotein E4; CDR – Clinical Dementia Rating; CDR-SB – Clinical Dementia Rating–Sum of Boxes; CSF – cerebrospinal fluid; C-SSRS – Columbia suicide severity rating scale; ECG – electrocardiogram; GDS – Global deterioration scale; HRQol – Health-related quality of life; iARDS – Integrated Alzheimer's disease rating scale; MCI – mild cognitive impairment; MMSE – Mini mental state examination; MRI – magnetic resonance imaging NIA-AA - National Institute on Aging and the Alzheimer's Association; OLE – open-label extension; PET – positron emission tomography; QOL-AD – Quality of life in Alzheimer's disease; UK – United Kingdom; ZBI – Zarit's Burden Interview

* Detail on substudies available in Section B.2.3.2.

[a] Permitted in the OLE after consultation with the Medical Monitor.

[b] Short-term use permitted in the OLE after consultation with the Medical Monitor.

[c] During the study, a patient should not initiate, change doses, or stop dosing unless deemed medically necessary by the investigator/designee and in line with local standard of care. If a patient starts, changes doses, or stops any of these medications, the patient will continue with study visits and assessments to study completion.

[d] Use of memantine not be allowed at enrolment for patients in Japan.

[e] Low doses of benzodiazepines or other sedatives may be administered before MRI scans for patients who have claustrophobia. There must be no cognitive assessments within 72 hours after sedatives administration.

B.2.3.1.1 Trial outcomes

A description of each of the pre-specified primary, secondary, and exploratory outcomes for Clarity AD are presented in Table 9.

Table 9: Summary of scales used as endpoints in Clarity AD

Scale	Items/tasks/domains	Description and interpretation of results	Administered/reported by
Primary endpoint			

CDR-SB[65]	Six domains:
	• Cognition:
	  ○ Memory
	  ○ Orientation
	  ○ Judgement/problem solving
	• Function:
	  ○ Community affairs
		Used to stage the severity of cognitive impairment via interview, discerning changes over time. A score ranging from 0 to 3 is assigned for each of the six domains, with higher scores indicating greater difficulty/severity. The sum of these provides a value ranging from 0 to 18, in increments of 0.5. Higher scores indicate greater disease severity (Section B.1.3.2). Moving from 0	Interview is administered by a qualified clinical professional, reported by the patient and study partner.

	○ Home/hobbies ○ Personal care	to 0.5 in a domain indicates progressing from unimpaired to impaired. Moving from 0.5 to 1 indicates progressing from slight impairment to loss of independence. Scores of 0.5 to 4.0 represent patients with MCI and scores of 4.5 to 9.0 represent mild AD patients. Scores of 9.5 to 15.5 represent moderate AD, and scores of 16.0 to 18.0 indicate severe AD.[66]	
Secondary endpoints			
ADAS-Cog14[141,142]	14 items (scoring range): • Word recall (0-10) • Naming objects and fingers (0-4) • Commands (0-5) • Constructional praxis (0-5) • Ideational praxis (0-5) • Orientation (0-8) • Word recognition (0-12) • Language (0-5) • Comprehension of spoken language (0-5) • Word finding difficulty (0-5) • Remembering test instructions (1-5) • Delayed word recall (0-10) • Maze (0-5) • Digit cancellation task (0-5)	Used to screen the patient for cognitive impairment via interview. Includes 14 items that include both patient-completed tests and observed-based assessments that assess cognition via memory, language, and praxis. Includes three additional items to the ADAS-Cog11 scale which may be more likely to be affected in patients with early AD, thereby increasing the sensitivity of the scale in this population.[142] Points are summed by the test administrator for all the errors in each task of the ADAS-Cog to a total score ranging from 0 to 90. The score is intended to capture the entire clinical course of AD, with higher scores indicating greater dysfunction (90, most severe and 0, least impairment). Typical range in early AD patients is 10 to 30.	Score is administered by clinician and includes both patient-completed tests and assessments observed by the clinician.
ADCOMS[143]	12 items (scoring range, weighting factor): • ADAS-Cog14: ○ Delayed word recall (0-10, 0.008) ○ Orientation (0-8, 0.017) ○ Word recognition (0-12, 0.004) ○ Word finding difficulty (0-5, 0.016)	Used to screen the patient for cognitive and functional impairment via interview. Contains a total of 12 cognitive and functional items, including four items from the ADAS-Cog14, two items from the MMSE, and all six items from the CDR-SB. Each task is weighted using partial least-squares regression according to their relative contribution to	Score is administered by clinician, self-reported by patient.

	• MMSE
	  ○ Orientation to time (0-5, 0.042)
	  ○ Drawing (0-1, 0.038)
	• CDR-SB
	  ○ Memory (0-3, 0.059)
	  ○ Orientation (0-3, 0.078)
	  ○ Judgement/problem solving (0-3, 0.069)
	  ○ Community affairs (0-3, 0.109)
	  ○ Home and hobbies (0-3, 0.089)
	  ○ Personal care (0-3, 0.054)
		detecting clinical progression in patients' early stages of AD (see weighting on the left). Values range from 0 to 1.97. Higher scores are indicative of greater impairment.	

ADCS MCI-ADL[144]	18 items: • Use a telephone, talk about current events, use household appliance, travel, balance banking, watch television, go shopping, read more than 5 minutes, find personal belongings, make a meal, select first clothes, clean room, perform pastime, keep appointments, write things down, clean laundry, left on his/her own, getting dressed.	Used to assess the level of functional integrity in early AD by assessing the performance of basic and instrumental activities of daily living by the patient via questionnaire. Functional evaluation scale that assesses the ability of patients to perform ADLs through a structured questionnaire administered to a carer by a clinician. A score ranging from 0 to 53 is given based on the patient's degree of independence in performing specific tasks. Lower scores are indicative of greater impairment. The care partner also reports function observed over the previous four weeks. Typical range in early AD patients is 35 to 45.	Score is administered by clinician, caregiver-reported.

Global CDR[65]	Six domains:
	• Cognition:
	  ○ Memory
	  ○ Orientation
	  ○ Judgement/problem solving
	• Function:
	  ○ Community affairs
	  ○ Home/hobbies
	  ○ Personal care
		The scores from the six domains of the CDR-SB are inputted into an algorithm which generates a score ranging from 0 to 3. Outcomes of this score are five possible stages: no cognitive impairment (CDR = 0), MCI (CDR = 0.5), mild dementia due to AD (CDR = 1), moderate dementia due to AD (CDR = 2), and severe dementia due to AD (CDR = 3).	Score is administered by a qualified clinical professional, reported by the patient and study partner.

HRQoL endpoints			
EQ-5D-5L[145]	Five dimensions: • Mobility • Self-care • Pain/discomfort • Usual activities • Anxiety/depression	Encompasses both a five-question descriptive system and a visual analogue score (VAS) assessment. The descriptive system comprises five dimensions aimed at reflecting the overall health of the individual (visible on the left), with each dimension being rated on a scale ranging from 1 to 5 (where 1 signifies no issues, 2 indicates minor problems, 3 represents some problems, 4 denotes severe problems, and 5 signifies extreme problems) for each question. The EQ-5D-5L VAS score measures the self-assessed health status of the respondent on a graduated scale from 0 to 100, where higher scores correspond to a greater level of HRQoL.	Patient, study partner as a proxy, and study partner.
QOL-AD[146,147]	13 terms: • Physical health, energy, mood, living situation, memory, family, marriage, friends, self as a whole, ability to do chores, ability to do things for fun, money, life as a whole	Used to assess the global quality of life in an AD patient via interview. A preference-based measure which uses four-point scale to rate a variety of life domains, including the patient's physical health, mood, relationships, and ability to complete tasks. Response options include 1 (poor), 2 (fair), 3 (good) and 4 (excellent). Each item is summed to give a total score of 13–52, with higher scores indicating better QoL.	Patient, study partner as a proxy.
ZBI[148]	22 terms: • Help, self-time, stress, embarrassment, anger, relationship, future, dependence, strain, health impacts, privacy, social life, uncomfortable, expectation, money, care duration, control, care delegation, uncertainty, doing more, better job, overall burden	Used to assess caregiver burden via interview, evaluating the stresses experienced by care partners of patients with AD. Each item on the interview is a statement which the caregiver is asked to endorse using a five-point scale. Response options range from 0 (never) to 4 (always). Scores are summed to give a total score out of 88. 0-21: no to mild burden. 21-40: mild to	Study partner.

		moderate burden. 41-60: moderate to severe burden. ≥ 61: severe burden.	

Abbreviations: AD – Alzheimer's disease; ADAS-Cog14 – Alzheimer's Disease Assessment Scale-Cognitive subscale; ADCOMS – Alzheimer's disease composite score; ADCS MCI-ADL – Alzheimer's Disease Cooperative Study – Activities of Daily Living for Mild Cognitive Impairment; CDR – Clinical Dementia Rating; CDR-SB – Clinical Dementia Rating – Sum of Boxes; MMSE – Mini mental state examination; QOL-AD – Quality of life in Alzheimer's disease; VAS – visual analogue scale; ZBI – Zarit's Burden Interview.

B.2.3.1.2 ARIA management

Amyloid-related imaging abnormalities are seen on brain magnetic resonance imaging (MRI) which occur naturally in patients with AD.[149,150] Increased occurrence of ARIA is often associated with therapies that remove Aβ species. ARIA can present as brain oedema or sulcal effusion (ARIA-E) or as haemosiderin deposits resulting from brain haemorrhage, either microhaemorrhage (< 1 centimetre (cm)) within the brain tissue or superficial siderosis on the pial surface (ARIA-H).[151] ARIA are transient and asymptomatic in most cases, with ARIA-E typically occurring in early stages of treatment with monoclonal antibodies that remove Aβ species, while ARIA-H may occur at any point during treatment due to the natural nature of its occurrence. The risk of ARIA generally decreases after the initial first three months of treatment with an anti-amyloid therapy, and ARIA usually resolve without the need for concomitant treatment.[149,152] No systematic data exist on potential treatments for ARIA.[152]

ARIA is a consequence of the presence of amyloid in cerebral blood vessel walls (cerebral amyloid angiopathy [CAA]). Microhaemorrhage, superficial siderosis, and uncommon intracerebral haemorrhage greater than 1 cm can result spontaneously in AD due to vascular remodelling with loss of vascular amyloid and smooth muscle, fibrinoid necrosis, and activation of astrocytes and microglia.[153] Anti-amyloid therapies may remove vascular amyloid and thus increase permeability to fluid (ARIA-E) or blood products (ARIA-H). Hypointensity on blood-sensitive sequences, including gradient echo or susceptibility weighted imaging MRI, associated with microhaemorrhages and haemosiderin deposits are typical of ARIA-H and are used for detection of ARIA-H. In patients treated with an anti-amyloid therapy, ARIA-H may occur concurrently with ARIA-E events.[152]

Accumulation of fluid in the brain's extracellular spaces due to increased permeability of blood vessels, known as vasogenic oedema, occurs in ARIA-E. This can lead to localised swelling. Symptomatic ARIA-E is relatively uncommon, however in some cases ARIA-E can cause clinical symptoms such as headache, confusion, or neurological deficits, depending on the severity of the oedema.[154] Throughout this document, ARIA-E refers to both isolated ARIA-E and ARIA-E concurrent with ARIA-H.

In the Clarity AD core study, any patients who developed a single macrohaemorrhage, multiple (>10) microhaemorrhages cumulatively, symptomatic cerebral microhaemorrhages, or symptomatic superficial siderosis had treatment administration temporarily stopped, and an additional safety visit and MRI at approximately 30 days after radiographic features were first identified. All patients who experienced these events had further safety visits approximately every 30 days until ARIA-H or intracerebral haemorrhage had stabilised radiographically and symptoms (if any) had resolved, then administration of treatment continued. Patients who developed asymptomatic, radiographically mild ARIA-E continued the treatment

uninterrupted but had an additional safety visit and MRI at approximately 30 days, 60 days, and 90 days after the MRI features were first identified. Patients continued with treatment if their ARIA-E did not worsen radiologically and remained asymptomatic. If their ARIA-E developed to a moderate or severe manifestation, or became symptomatic, or patients presented acutely with symptoms or radiographically moderate or severe ARIA-E, patients were temporarily stopped from treatment administration and only resumed treatment if ARIA-E resolved radiographically and symptoms (if any) resolved. US appropriate use recommendations for continued lecanemab treatment for patients with ARIA-E and ARIA-H at different severities are provided in Figure 10.

Figure 10: Lecanemab treatment recommendations for patients with ARIA by severity of symptoms and severity of the radiographic ARIA-E or ARIA-H on MRI

	Symptom Description			
	No Symptoms	**Mild Symptoms**	**Moderate Symptoms**	**Severe Symptoms**
Severity of Changes Observed on MRI	None	Discomfort noted; no disruption of daily activity	Discomfort sufficient to reduce or affect normal daily activity	Incapacitating, with inability to work or to perform normal daily activity
ARIA-E on MRI				
Mild	Continue dosing	Suspend dosing	Suspend dosing	Discontinue dosing
Moderate	Suspend dosing	Suspend dosing	Suspend dosing	Discontinue dosing
Severe	Discontinue dosing	Discontinue dosing	Discontinue dosing	Discontinue dosing
ARIA-H on MRI				
Mild	Continue dosing	Suspend dosing	Suspend dosing	Discontinue dosing
Moderate	Suspend dosing	Suspend dosing	Suspend dosing	Discontinue dosing
Severe	Discontinue dosing	Discontinue dosing	Discontinue dosing	Discontinue dosing

Abbreviations: ARIA-E – amyloid-related imaging abnormality-oedema/effusion; ARIA-H – amyloid-related imaging abnormality-microhaemorrhage and haemosiderin deposit; MRI – magnetic resonance imaging
Source: Cummings et al., 2023[155]

B.2.3.2 Substudies

Three longitudinal substudies were conducted during Clarity AD through amyloid PET, CSF biomarker assessments, and tau PET to assess engagement and effect on downstream processes in the amyloid cascade, including effect on tau pathology, inflammation and synapse biomarkers. Participation in these substudies was optional and required separate consent that did not affect enrolment or treatment in the core study. Patients could participate in one or more substudies, however patients who were on anticoagulant therapy were not eligible to participate in the CSF biomarker substudy due to contraindication to lumbar puncture. Additionally, the longitudinal tau PET substudy was offered only to patients who:

- Enrolled at sites able to participate (based on the site's geographical location or proximity to the tau PET ligand manufacturing sites), and
- Had an amyloid positive study-specific PET scan at baseline.

B.2.3.3 Patient demographics and baseline characteristics

Demographic and other baseline characteristics of randomised patients are presented in Table 10. Of the 1,795 patients in the SAS (Table 13 in Section B.2.4), patients were predominantly white ([redacted]%) with a mean age of [redacted] years. The proportion of patients with MCI and mild AD was similar between the two groups with [redacted]% of MCI patients in the lecanemab arm versus [redacted]% in the placebo arm and [redacted]% of mild AD patients in the lecanemab arm versus [redacted]% in the placebo arm. Gender was well-balanced across the trial arms ([redacted]% female patients in the lecanemab arm and [redacted]% in the placebo arm), as was use of AD symptomatic medication ([redacted]% patients in the lecanemab arm and [redacted]% in the placebo arm). *APOE4* is a gene associated with an increased risk of AD, earlier age of onset of AD, increased severity of CAA, and increased risk of haemorrhage due to CAA.[7] Homozygous *APOE4* carriers are thought to be at a greater risk of AD compared to heterozygous carriers.[156] *APOE4* status was similar between the two groups, with a similar split between carriers, heterozygous, and homozygous (lecanemab: [redacted]%, [redacted]%, [redacted]%; placebo: [redacted]%, [redacted]%, [redacted]%, respectively).

Table 10: Clarity AD patient demographics and baseline characteristics (SAS)

	Lecanemab (n=898)	**Placebo (n=897)**	**Total patients (1,795)**
Mean age, years (SD) [a]	[redacted]	[redacted]	[redacted]
Female, n (%)	[redacted]	[redacted]	[redacted]
Race, n (%)			
White	[redacted]	[redacted]	[redacted]
Black or African American	[redacted]	[redacted]	[redacted]
Asian	[redacted]	[redacted]	[redacted]
American Indian or Alaska native	[redacted]	[redacted]	[redacted]
Native Hawaiian or other Pacific Islander	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]
Not reported	[redacted]	[redacted]	[redacted]
APOE4 carrier status (Laboratory), n (%)			
Carriers	[redacted]	[redacted]	[redacted]

Heterozygous	[redacted]	[redacted]	[redacted]
Homozygous	[redacted]	[redacted]	[redacted]
Use of AD symptomatic medication at baseline (CRF), n (%)			
Yes	[redacted]	[redacted]	[redacted]
Clinical subgroup (CRF), n (%)			
MCI due to AD	[redacted]	[redacted]	[redacted]
Mild AD dementia	[redacted]	[redacted]	[redacted]
Number of years of disease since diagnosis			
n	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]
Median (range)	[redacted]	[redacted]	[redacted]
Number of years since onset of symptoms			
n	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]
Median (range)	[redacted]	[redacted]	[redacted]
Age at onset of symptoms (years)			
n	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]
Median (range)	[redacted]	[redacted]	[redacted]

Percentages are based on the total number of patients in relevant treatment group.
Abbreviations: AD – Alzheimer's disease, *APOE4* – apolipoprotein E4, CRF – case report form, MCI – mild cognitive impairment, Min – minimum, Max – maximum.
[a] Age was calculated at date of informed consent.

Baseline characteristics from the primary trial publication (as listed in Appendix N) were presented to UK clinical experts in an advisory board held in May 2023 and the Clarity AD population was deemed generalisable to UK clinical practice.[3,137]

B.2.3.4 Patient disposition and primary reason for discontinuation

Of the 1,795 randomised patients, 1,440 patients completed core study treatment (lecanemab 729/898; placebo 757/897).[135] The rate of discontinuation from treatment was similar across arms (lecanemab 199 [22.2%]; placebo 156 [17.4%]). The reasons for discontinuation from treatment were similar across treatment arms, with the most common being adverse events (lecanemab 69 [7.7%]; placebo 29 [3.2%]) and withdrawal of consent (lecanemab 69 [7.7%]; placebo 71 [7.9%]) as presented in Table 11.

Table 11: Patient disposition and primary reason for discontinuation from study treatment, Clarity AD

	Number of patients, n (%)		
	Lecanemab (n=898)	**Placebo (n=897)**	**Total (n=1,795)**
Treated	898 (100.0)	897 (100.0)	1,795 (100.0)
Completed core study treatment	699 (77.8)	741 (82.6)	1,440 (80.2)
Discontinued from treatment	199 (22.2)	156 (17.4)	355 (19.8)
Primary reason for discontinuation from treatment			
Adverse event	69 (7.7)	29 (3.2)	98 (5.5)
Patient choice	33 (3.7)	28 (3.1)	61 (3.4)
Pregnancy	0 (0.0)	0 (0.0)	0 (0.0)
Inadequate therapeutic effect	0 (0.0)	1 (0.1)	1 (0.1)
Lost to follow-up	1 (0.1)	3 (0.3)	4 (0.2)
Withdrawal of consent	69 (7.7)	71 (7.9)	140 (7.8)
Study terminated by sponsor	0 (0.0)	0 (0.0)	0 (0.0)
Other	27 (3.0)	24 (2.7)	51 (2.8)

Patients who completed Visit 42 are considered as the patients who completed core study treatment. If patients have missing primary reason for discontinuation from treatment, they are counted under “Other” for discontinuation reason.
Source: Table 14.1.1.4.1, Clarity AD CSR[135]

Of the 1,795 randomised patients, 1,486 patients completed the core study (lecanemab 729/898; placebo 757/897).[135] The rate of discontinuation from the study was similar across arms (lecanemab 169 [18.8%]; placebo 140 [15.6%]). The reasons for discontinuation from the study were similar across treatment arms, with the most common being adverse events (lecanemab 51 [5.7%]; placebo 28 [3.1%]) and withdrawal of consent (lecanemab 69 [7.7%]; placebo 67 [7.5%]) as presented in Table 12.

Table 12: Primary reason for discontinuation from the study, Clarity AD

	Number of patients, n (%)		
	Lecanemab (n=898)	**Placebo (n=897)**	**Total (n=1,795)**
Treated	898 (100.0)	897 (100.0)	1,795 (100.0)

Completed core study	729 (81.2)	757 (84.4)	1,486 (82.8)
Discontinued from core study	169 (18.8)	140 (15.6)	309 (17.2)
Primary reason for discontinuation			
Adverse event	51 (5.7)	28 (3.1)	79 (4.4)
Patient choice	26 (2.9)	24 (2.7)	50 (2.8)
Pregnancy	0 (0.0)	0 (0.0)	0 (0.0)
Inadequate therapeutic effect	0 (0.0)	0 (0.0)	0 (0.0)
Lost to follow-up	4 (0.4)	5 (0.6)	9 (0.5)
Withdrawal of consent	69 (7.7)	67 (7.5)	136 (7.6)
Study terminated by sponsor	0 (0.0)	0 (0.0)	0 (0.0)
Other	19 (2.1)	16 (1.8)	35 (1.9)

Patients who completed Visit 42 are considered as the patients who completed core study. If patients have missing primary reason for discontinuation, they are counted under “Other” for discontinuation reason.
Source: Table 14.1.1.3.2, Clarity AD CSR[135]

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

B.2.4.1 Analysis sets

Patient data sets analysed in Clarity AD are described in Table 13. Efficacy analyses were performed on the intent-to-treat (ITT) Full Analysis Set+ (FAS+), and safety analyses on the SAS.

Table 13: Analysis Sets (Randomised Set) – Core study

Analysis set	Definition		Number of patients, n (%)		
			Placebo	Lecanemab	Total
SAS	All allocated patients who received at least one dose of study drug. At least one laboratory, vital sign, or ECG measurement obtained subsequent to at least one dose of study drug was required for inclusion in the analysis of each specific parameter. To assess change from baseline, a baseline measurement was also required. This was the analysis population used for all safety analyses which was based on as-treated principle		897 (100)	898 (100)	1795 (100)
ITT FAS+	Randomised patients who received at least one dose of study drug, and who had a baseline assessment and at least one post-dose primary efficacy measurement.		875 (97.5)	859 (95.7)	1734 (96.6)
ITT FDA FAS	Randomised patients who received at least one dose of study drug, who had a baseline assessment and at least one post-dose primary efficacy measurement, and who were not randomised on or before the end date of dosing hold at the sites which had dosing hold with six or more weeks (≥42 days, which is equal to three consecutive doses) during COVID-19 period of 01 Mar to 31 Jul 2020. The baseline assessment was defined as the last measurement before the first dose of lecanemab.		[redacted]	[redacted]	[redacted]
Per Protocol Analysis Set	Subset of patients in the ITT FDA FAS who did not miss three or more consecutive doses during their first six months in the study.		[redacted]	[redacted]	[redacted]
PK Analysis Set	Patients with at least one quantifiable lecanemab serum concentration (analysis set for serum) or CSF concentration (analysis set for CSF) with a documented dosing history.	Serum	[redacted]	[redacted]	[redacted]
		CSF	[redacted]	[redacted]	[redacted]
PD Analysis Set	Patients who had received at least one dose of study drug, and who had sufficient PD data to derive at least one PD parameter (had baseline and at least one post-dose assessment)	Amyloid PET	[redacted]	[redacted]	[redacted]
		Tau PET	[redacted]	[redacted]	[redacted]
		Plasma	[redacted]	[redacted]	[redacted]
		CSF	[redacted]	[redacted]	[redacted]
		vMRI	[redacted]	[redacted]	[redacted]

Abbreviations: CSF – Cerebrospinal fluid; ECG – Electrocardiogram; FAS – Full Analysis Set; FDA – Food and Drug Administration; ITT – Intent-to-treat; MRI – magnetic resonance imaging; PD – Pharmacodynamic; PET – Positron emission tomography; PK – Pharmacokinetic; SAS – Safety Analysis Set; vMRI – volumetric magnetic resonance imaging.

B.2.4.2 Statistical analyses

The primary objective of Clarity AD was to evaluate the change from baseline in the CDR-SB at 18 months of treatment with lecanemab, compared to placebo, in patients with early AD. Based on Study 201, it was estimated that approximately 1,766 patients would be needed to achieve 90% power to detect the treatment difference between placebo and lecanemab in all patients using a two-sample t-test at a significance level of two-sided alpha=0.05. The primary analysis was performed using a mixed effects model with repeated measures (MMRM) in the ITT population. The MMRM included treatment group, visit, stratification variables, baseline CDR-SB-by-visit interaction and treatment group-by-visit interaction as fixed effects, and baseline CDR-SB as a covariate. An unstructured covariance matrix was employed to model the covariance of within-patient effect. If the MMRM failed to converge then a covariance structure with fewer parameters was employed. Supplementary analysis was conducted to assess the robustness of the primary analysis. The secondary endpoints, change from baseline in amyloid PET using Centiloids, ADAS-Cog14, ADCOMS, and ADCS MCI-ADL, were also analysed using MMRM. Statistical methods used in Clarity AD are discussed in further detail in Table 14.

Table 14: Clarity AD statistical analysis

Hypothesis objective	The null hypothesis was that there was no difference in the mean change from baseline in CDR-SB at 18 months between lecanemab and placebo. The null hypothesis was tested for lecanemab versus placebo at a significance level of two-sided alpha=0.05.
Sample size, power calculation	The sample size for Clarity AD was estimated based on comparison of lecanemab and placebo with respect to the primary efficacy endpoint, change from baseline in CDR-SB at 18 months. Based on data from Study 201[157], an estimated standard deviation of the change from baseline CDR-SB at 18 months in placebo was 2.031 and an estimated treatment difference was 0.373 in all patients. Therefore, assuming an estimated 20% dropout rate at 18 months in this study, a total sample size of 1,566 patients, including 783 patients in placebo and 783 patients in lecanemab, had 90% power to detect the treatment difference between placebo and lecanemab in all patients using a 2-sample t test at a significance level of 2-sided alpha=0.05. Considering approximately 200 patients who missed three or more consecutive doses due to COVID-19 pandemic, in agreement with Health Authorities (FDA, European Medicines Agency [EMA] & Japanese Pharmaceuticals and Medical Devices Agency [PMDA]), an additional approximately 200 patients were randomised to retain 90% power, for a total sample size of approximately 1,766 randomised patients. To ensure that the study population was consistent with prior data used in the specified power calculations, approximately 70% of total number of patients randomised were *APOE4* carriers.
Statistical analysis	**Primary efficacy analysis** • The primary analysis of the change from baseline in CDR-SB at 18 months were performed to compare lecanemab with placebo

	using a mixed effects model with repeated measures (MMRM) on the ITT FAS+ dataset. • The MMRM included baseline CDR-SB as a covariate, with treatment group, visit, stratification variables (clinical subgroup, use of AD symptomatic medication at baseline, *APOE4* carrier status, and geographical region), baseline CDR-SB-by-visit, and treatment group-by-visit interaction as fixed effects. For stratification variables, actual data (laboratory data for *APOE4* carrier status, case report form [CRF] data for clinical subgroup and use of AD symptomatic medication at baseline, and interactive voice and web response system (IxRS) data for geographical region) were used. An unstructured covariance matrix was employed to model the covariance of within-patient effect; if MMRM failed to converge then a covariance structure with fewer parameters was employed until the MMRM converged. Covariance structures tested were Heterogeneous Toeplitz, Heterogeneous Compound Symmetry, Toeplitz, and Compound Symmetry. If a structured covariance was used, then the sandwich estimator was used to estimate variance of the treatment effect estimator. **Key secondary efficacy analyses** • Change from baseline in amyloid PET using Centiloids at 18 months for brain amyloid levels was analysed using the following in the MMRM instead of baseline CDR-SB and baseline CDR-SB-by-visit interaction: o Baseline amyloid PET using Centiloids o Baseline amyloid PET using Centiloids-by-visit interaction • Following the same pattern as change from baseline in amyloid PET, change from baseline in ADAS-Cog14, ADCOMS, ADCS MCI-ADL at 18 months were analysed using the same MMRM as CDR-SB to compare lecanemab and placebo on the ITT FAS+ dataset, using baseline value corresponding to the response variable and baseline value-by-visit interaction in the model. **Exploratory efficacy analyses** • Rate of change over time (mean slope) based on change from baseline in the CDR-SB was analysed using a linear mixed effects (LME) model for multivariate normal data derived from a random coefficient model (slope analysis) on the ITT FAS+ dataset, where the mean slope in each group depends on a continuous assessment time. The LME model included assessment time and treatment group-by-assessment time as covariates with random intercept and slope. • Time to worsening of global CDR score by 18 months was analysed using Cox regression model for treatment effect adjusting for randomisation stratification factors on the ITT FAS+ dataset. Time to worsening of a global CDR score was defined as time from randomisation to worsening of the global CDR score (i.e., the first worsening in two consecutive scheduled visits). • Change from baseline in EQ-5D-5L, QOL-AD, and ZBI at 18 months were analysed on the ITT FAS+ dataset using the MMRM described for CDR-SB, using baseline value corresponding to the

	response variable and baseline value-by-visit interaction in the model.
Data management and patient withdrawals	The primary and secondary analyses included all observed post-baseline data of the change from baseline without imputation of missing values.* Other statistical methods for missing data such as multiple imputation were also performed as sensitivity analyses.
Interim analyses	No interim analysis was planned or conducted for this study.

Abbreviations: AD – Alzheimer's disease; ADAS-Cog14 – Alzheimer's Disease Assessment Scale-Cognitive subscale; ADCOMS – Alzheimer's disease composite score; ADCS MCI-ADL – Alzheimer's Disease Cooperative Study – Activities of Daily Living for Mild Cognitive Impairment; *APOE4* – apolipoprotein E4; CDR – Clinical Dementia Rating; CDR-SB – Clinical Dementia Rating – Sum of Boxes; CRF – case report form; EMA – European Medicines Agency; FDA – Food and Drug Administration; FAS – Full Analysis Set; iARDS – Integrated Alzheimer's disease rating scale; IxRS – Interactive voice and web response system; LME – linear mixed effects; MHLW – Japanese Ministry of Health, Labor and Welfare; MMRM – mixed effects model with repeated measures; PD – pharmacodynamic; PET – positron emission tomography; PMDA – Pharmaceuticals and Medical Devices Agency; QOL-AD – Quality of life in Alzheimer's disease; ZBI – Zarit's Burden Interview
*Post-baseline refers to any visit after month zero from the Clarity AD core study.

B.2.5 Critical appraisal of the Clarity AD trial

Quality assessment of Clarity AD was conducted using the NICE single technology assessment: User guide for company evidence submission template, adapted from Systematic reviews: Centre for Reviews and Dissemination's guidance for undertaking reviews in health care (University of York Centre for Reviews and Dissemination) with results presented in Table 15.[158]

Randomisation and stratification were carried out appropriately, concealment of treatment allocation was adequate, and the groups were similar at the study onset in terms of prognostic factors. There were no unexpected imbalances in dropouts between the groups and no evidence that the authors measured more outcomes than they reported. An ITT analysis was conducted, and appropriate methods were used to account for missing data. Overall, the quality of Clarity AD can be deemed high.

Table 15: Clarity AD quality assessment results

Questions	Clarity AD[135]
Was randomisation carried out appropriately?	**Yes:** Patients were assigned to treatments, (allocated 1:1; lecanemab:placebo), based on a computer-generated randomisation scheme that was reviewed and approved by an independent statistician. Patients were stratified according to clinical subgroup; presence or absence of ongoing approved AD treatment (e.g., AChEIs, memantine, or both); *APOE4* status (i.e., *APOE4* carrier or noncarrier); and geographical region.
Was the concealment of treatment allocation adequate?	**Yes.** Randomisation data was kept strictly confidential, filed securely by an appropriate group with the sponsor or CRO and accessible only to authorised persons (e.g., Eisai Global Safety) until the time of unblinding, per SOP.

Questions	Clarity AD[135]
Were the groups similar at the outset of the study in terms of prognostic factors?	**Yes:** There was no significant difference in the baseline characteristics reported between the treatment arms.
Were the care providers, participants, and outcome assessors blind to treatment allocation?	**Yes:** During the core study phase, patients and all personnel involved with the conduct and interpretation of the study, including investigators, site personnel, and sponsor staff were blinded to the treatment codes.
Were there any unexpected imbalances in dropouts between groups?	**No:** There were no unexpected imbalances in dropouts between groups. Withdrawals by patient were similar in both arms (lecanemab 169/898 [18.8%]; placebo 140/897 [15.6%]).
Is there any evidence to suggest that the authors measured more outcomes than they reported?	**No:** No evidence to suggest that the authors measured more outcomes than they reported.
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	**Yes:** Efficacy analysis was performed using the FAS population. Following the intent-to-treat principle, patients were analysed according to the treatments and strata to which they were assigned at randomisation. For missing data: Missing values in all endpoint data were handled by the MMRM. Other statistical methods for missing data were also performed as sensitivity analyses (detailed in Table 14).

Abbreviations: AChEI – acetylcholinesterase inhibitor; AD – Alzheimer's disease; *APOE4* – apolipoprotein E4; CRO – contract research organisation; FAS – Full Analysis Set; MMRM – mixed effects model with repeated measures; SOP – standard operating procedure.

B.2.6 Clinical effectiveness results of the relevant trials

The following sections present the clinical effectiveness results from Clarity AD. Results are presented for the core study period from 27 March 2019 to 25 August 2022, on which the key publication by van Dyck et al. was based.[3] All 'change from baseline' results were analysed using the MMRM described in B.2.4.2. Missing values were not imputed and assumed to be missing at random. Percentage difference was calculated as adjusted mean difference divided by adjusted mean for placebo group. For each timepoint analysis, the observations described at all post-treatment visits are included in the MMRM to provide the adjusted mean at each post-treatment visit.

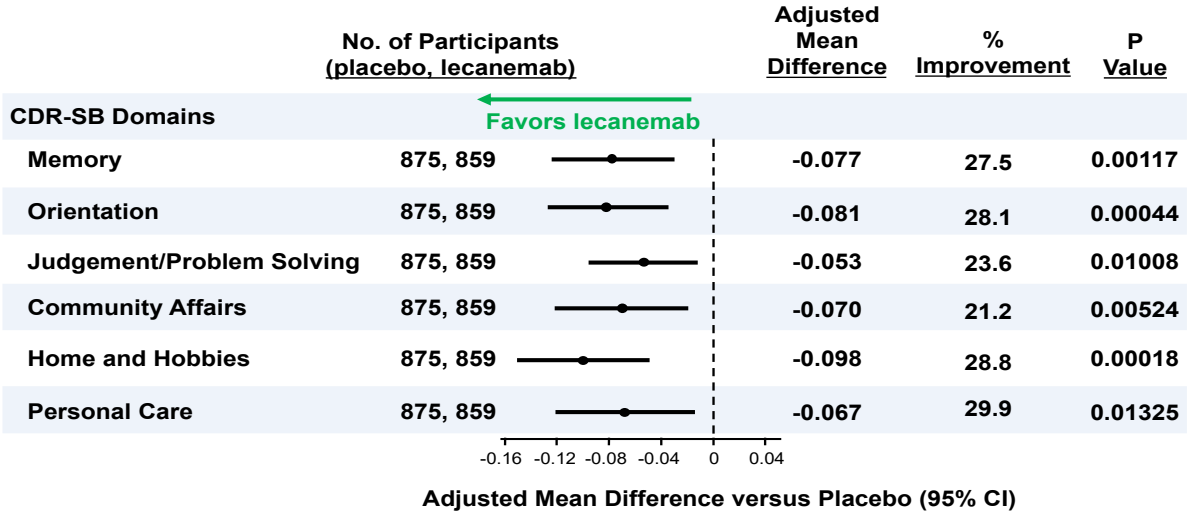
For a detailed description of each primary and secondary outcome presented in this section, refer to Section B.2.3.1.1, Table 9.

B.2.6.1 Primary efficacy outcome: CDR-SB

The primary endpoint was the adjusted mean difference of the change from baseline in CDR-SB at 18 months between lecanemab and placebo in the ITT FAS+. CDR-SB measures six domains of cognition and function that patients and caregivers identify as important to represent autonomy and a sense of self, including memory, orientation, judgement and problem solving, community affairs, home and hobbies, and personal care (Table 9).

Lecanemab showed statistically significant benefit versus placebo across all six CDR-SB domains (Memory: $p<0.005$; Orientation: $p<0.0005$; Judgement/Problem Solving: $p<0.05$; Community Affairs: $p<0.05$; Home and Hobbies: $p<0.0005$; Personal Care: $p<0.05$), demonstrating that lecanemab provides manifold benefits to patients (Figure 11).

Figure 11: Adjusted mean difference versus placebo in CDR-SB by domain – ITT FAS+



Abbreviations: CDR-SB – Clinical Dementia Rating–Sum of Boxes; CI – confidence interval; FAS – Full Analysis Set; ITT – intent-to-treat.

The adjusted mean treatment difference for lecanemab compared to placebo at 18 months across all domains of -0.451 (1.213 for lecanemab versus 1.663 for placebo) was highly statistically significant ($p=0.00005$), reflecting 27.1% less decline in the CDR-SB (Table 16). This is a clinically meaningful slowing of decline, based on the peer-reviewed literature, statistical principles, and guidance from regulatory authorities under which Clarity AD was designed.[3,159–163] Further interpretation of these data is given in Section B.2.12.1.

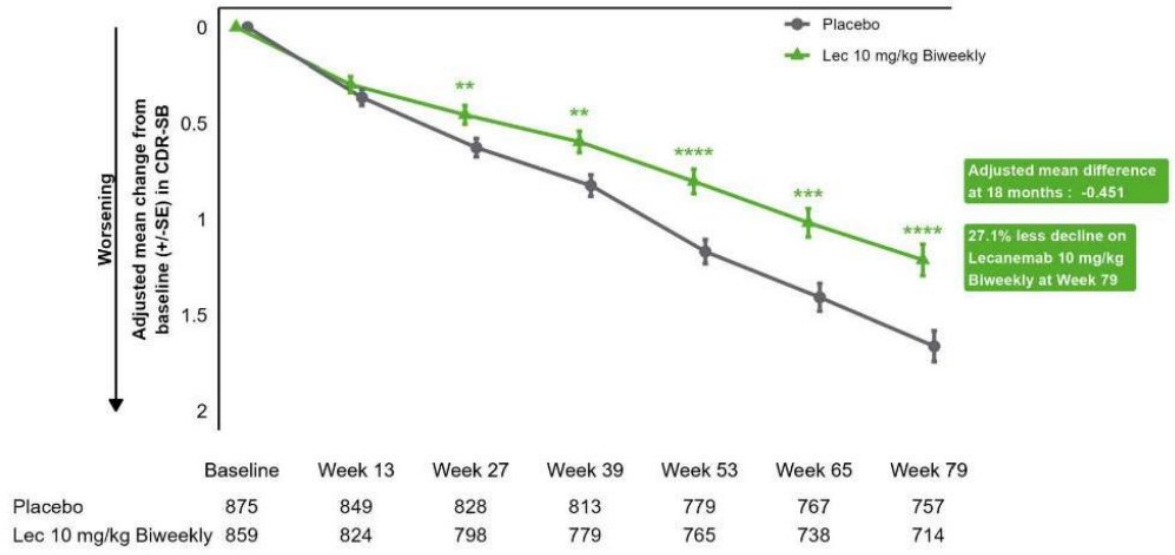
Table 16: Change from baseline in CDR-SB Score at 18 Months – MMRM – ITT FAS+

Statistic	Lecanemab (n=859)	Placebo (n=875)
Number of patients included in the MMRM	859	875
N (week 79)	714	757
Adjusted mean (SE)	1.213 (0.082)	1.663 (0.080)
Adjusted mean difference (lecanemab – placebo)	-0.451	
95% confidence interval (CI) for differences	-0.669, -0.233	
p-value	0.00005	
% Difference vs. placebo	-27.1%	

Source: Table 7, Clarity AD CSR[135]
Abbreviations: AD – Alzheimer's disease; *APOE4* – apolipoprotein E4; CDR-SB – Clinical Dementia Rating–Sum of Boxes; FAS – Full Analysis Set; ITT – intent-to-treat; MMRM – mixed model for repeated measures; N – number of patients at each visit; n – number of patients in treatment group; SE – standard error.

Lecanemab showed statistically significant differences in CDR-SB scores from as early as the earliest timepoint, six months, compared to placebo (p<0.01). The absolute difference in CDR-SB scores between lecanemab and placebo continued to increase over time, with highly statistically significant changes (all p<0.001) at 12, 15, and 18 months (Figure 12). The change from baseline in CDR-SB results for 3 to 15 months are shown in Table 60, Appendix O.1.2.

Figure 12: Adjusted mean change (±SE) from baseline in CDR-SB – ITT FAS+

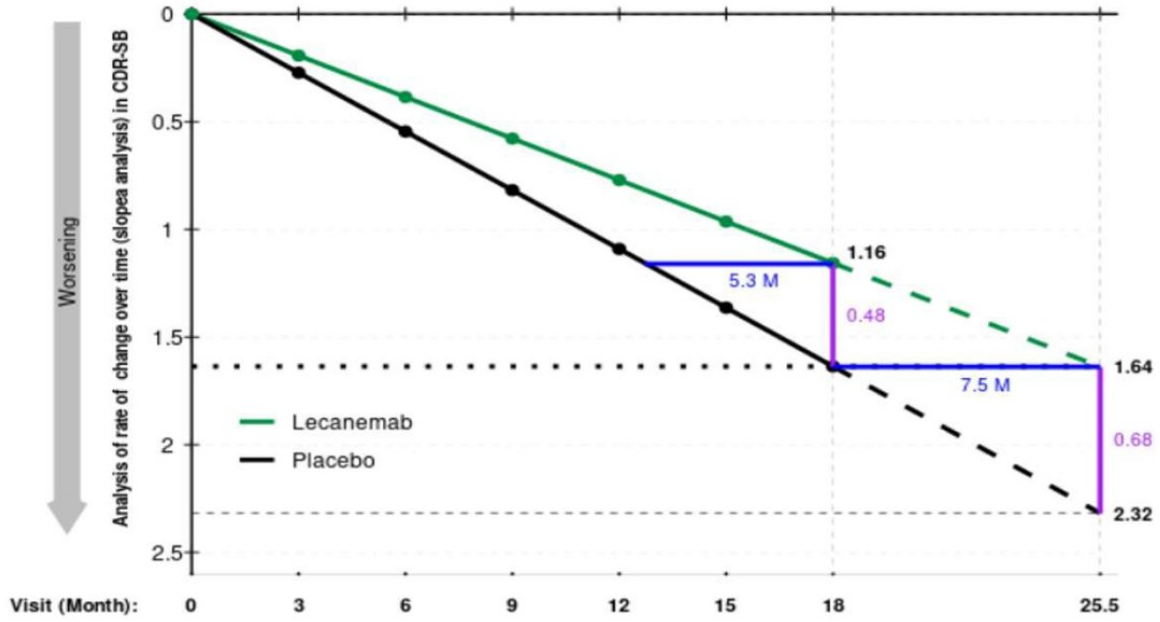


Source: Figure 3, Clarity AD CSR[135]
** p<0.01, *** p<0.001, **** p<0.0001.
Abbreviations: AD – Alzheimer's disease; *APOE4* – apolipoprotein E4; CDR-SB – Clinical Dementia Rating – Sum of Boxes; FAS – Full Analysis Set; ITT – intent-to-treat; kg – kilogram; Lec – lecanemab; mg – milligram; MMRM – mixed model for repeated measures.

A slope analysis was conducted to analyse this continuously increasing treatment difference beyond 18 months which translates the difference in CDR-SB into measures of 'time saved' or 'time preserved' for patients (Figure 13). An LME model

for multivariate normal data was derived from a random coefficient model (slope analysis) on the ITT FAS+, where the mean slope in each group depends on a continuous assessment time. The LME model included assessment time and treatment group-by-assessment time as covariates, with random intercept and slope. The analysis indicates an increasing separation over time between lecanemab and placebo, with a 29.3% slowing of slope on lecanemab annually compared to placebo (p=0.00001). This indicates that if effects observed in the core study continue beyond 18 months, lecanemab would not reach the 18-month placebo level of worsening until 7.5 months later, at approximately 25.5 months and this suggests preservation of CDR-SB by approximately 5.3 months relative to placebo at 18 months. This shows that with continued treatment, there is increasing time saved by patients.

Figure 13: Slope analysis of rate of change over time of CDR-SB – Linear mixed effects model – ITT FAS+



Source: Figure 4, Clarity AD CSR[135]
Abbreviations: CDR-SB – Clinical Dementia Rating – Sum of Boxes; FAS – Full Analysis Set; ITT – intent-to-treat; M – Months.

B.2.6.1.1 Sensitivity Analysis

The primary analysis of CDR-SB for the ITT population did not impute missing data and assumed data were missing at random. To test this and assess the robustness of the primary analysis, a series of sensitivity analyses were conducted using different assumptions about missing data, detailed in Appendix P.

Overall, the sensitivity and supplementary analyses were consistent with the primary analysis in confirming that lecanemab resulted in a statistically significant change from baseline in CDR-SB at 18 months, compared with placebo, regardless of

imputation method or changes to the MMRM. See Table 17 for full results of these analyses.

Table 17: Change from baseline in CDR-SB score at 18 months – ITT – Sensitivity and supplementary analyses*

#	Sensitivity analysis	Adjusted mean change from baseline (placebo)	Adjusted mean change from baseline (lecanemab)	Adjust mean difference (lecanemab – placebo)	95% CI for difference	*p*-value
1	Rank ANCOVA with missing data imputed via multiple imputation approach	NA	NA	-0.456**	[redacted]	<0.001
2	Primary MMRM repeated to evaluate impact of COVID-19	1.603	1.208	-0.394	[redacted]	<0.001
3	All randomised patients† (randomised set)	1.659	1.225	-0.434	[redacted]	<0.001
4	Randomisation stratification variables based on IxRS classification (ITT FAS+)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5	Primary MMRM with log-transformed endpoint as response variable (ITT FAS+)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
6	Primary MMRM excluding assessments after initiation/dose adjustment of symptomatic AD drug or treatment discontinuation (ITT FAS+)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
7	Primary MMRM on per protocol participants	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
8	Primary MMRM excluding assessments after occurrence of ARIA (ARIA-E or ARIA-H) (ITT FAS+)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
9	Primary MMRM excluding assessments after occurrence of ARIA-E (ITT FAS+)	1.672	1.169	-0.503	[redacted]	<0.001
10	Primary MMRM excluding assessments after occurrence of ARIA-H (ITT FAS+)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
11	Primary MMRM including APC as additional covariate (ITT FAS+)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AD – Alzheimer's disease; ANCOVA – analysis of covariance; APC – Alzheimer's prognostic covariate; ARIA – amyloid-related imaging abnormalities; ARIA-E – amyloid-related imaging abnormality-oedema/effusion; ARIA-H – amyloid-related imaging abnormality-microhaemorrhage and haemosiderin deposit; CDR-SB – Clinical Dementia Rating–Sum of Boxes; ITT – intent-to-treat; FAS+ – Full Analysis Set+; IxRS – interactive voice and web response system; MMRM – mixed model for repeated measures; NA – Not applicable.

*All analyses performed are the primary MMRM on CDR-SB except the rank ANCOVA. **Hodges-Lehmann non-parametric estimate of median difference. ***Hodges-Lehmann non-parametric estimate of median difference and asymptotic standard error are calculated and then combined using Rubin's rules to compute the CI. †All randomised patients (N=1,795) are included. Missing values for randomised patients but not in ITT FAS+ are imputed using placebo means at each visit.

B.2.6.2 Secondary efficacy outcomes

All key secondary endpoints including cognition, function, and biomarker changes (change from baseline at 18 months in amyloid PET Centiloids, ADAS-Cog14, ADCOMS, and ADCS MCI-ADL) yielded highly statistically significant results favouring lecanemab compared with placebo. See Section B.2.3.1.1, Table 9 for a full description of each endpoint. For all key secondary endpoints, separation emerged at the first timepoint (three months for amyloid PET using Centiloids, ADAS-Cog14 and ADCOMS, six months for ADCS MCI-ADL); statistically significant differences were observed for all endpoints by six months ([redacted]); and highly significant differences were observed beyond six months for all endpoints (p<0.001).

B.2.6.2.1 Amyloid PET using Centiloids

In the Clarity AD amyloid PET substudy, Centiloid values are presented by combining data across all PET tracers. The Centiloid scale is anchored at 0 (the mean amyloid level in young healthy people) and 100 (the mean amyloid level in mild-moderate AD). The extent of amyloid reduction is dependent on baseline amyloid levels, as shown in trials of other anti-amyloid therapies.[164,165] In Clarity AD, the baseline level in the lecanemab group was 77.9 Centiloids, reducing to [redacted] Centiloids at 18 months, a [redacted] Centiloid decrease (only patients with non-missing data at both baseline and the 18 months visit are included in the change from baseline summary statistics, Table 66, Appendix O1.6). This is below the threshold for amyloid negativity of approximately 30 Centiloids which is considered a 'normal' level, above which participants are considered to have elevated or 'higher than normal' brain amyloid.[166] The threshold for amyloid negativity was defined as amyloid PET standard uptake value ratio (SUVR)=1.17, which corresponds to 30 Centiloids.[167] This threshold lies in between the 25.0 to 35.7 Centiloid range for agreement with visual reads[168–171], and is aligned with both Centiloid thresholds for 'established Aβ pathology' as determined by histopathology[168], and p-tau/Aβ42 and CSF t-tau/Aβ42 thresholds.[172] Reducing amyloid levels in the early stages of AD could inhibit the 'trigger' leading to the toxicity and pathology seen in AD. See Section B.1.2 for more detail on the importance of amyloid clearance. In contrast, the baseline level in the placebo group was 75.0 Centiloids, increasing to [redacted] Centiloids at 18 months, a [redacted] Centiloid increase.

B.2.6.2.2 Patients converting to amyloid negativity

There was a statistically significant difference between lecanemab and placebo in the proportion of patients who converted to amyloid negativity by Centiloids, with a difference being seen as early as three months (lecanemab [redacted]% vs placebo [redacted]%, p=[redacted], Figure 14). This difference was maintained through to 18 months of treatment, with a highly statistically significant difference seen from as early as six months. Only [redacted]% of patients receiving placebo had achieved

amyloid negativity at 18 months compared to [redacted]% of patients who received lecanemab (p<[redacted], Figure 14).

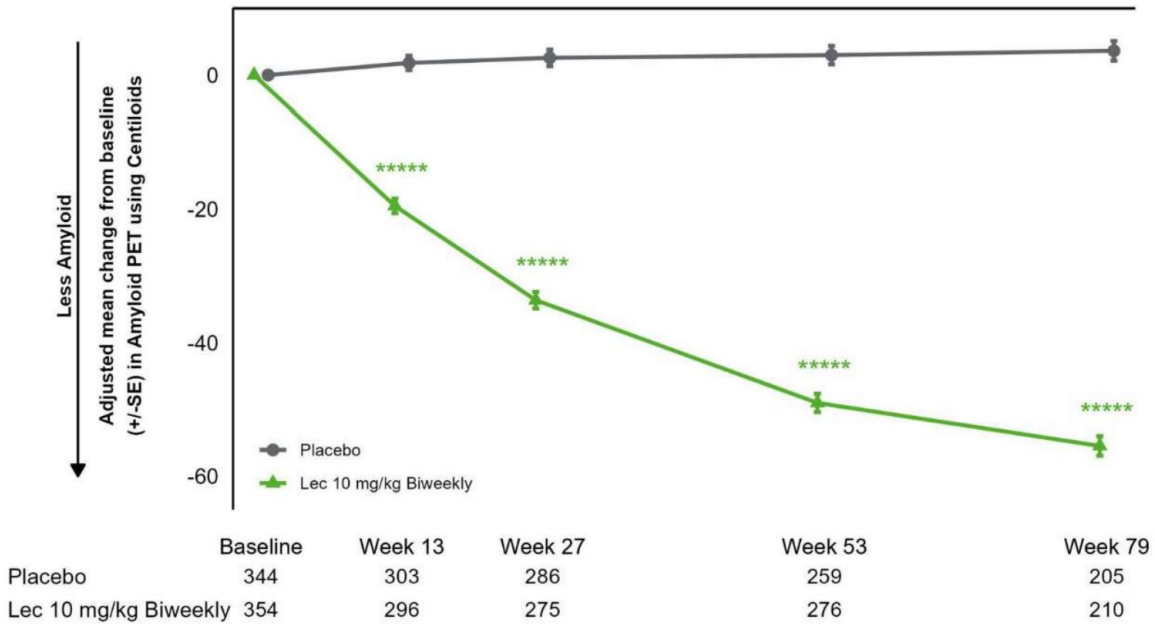
Figure 14: Proportion of patients who became amyloid negative by visit – PD analysis set

Abbreviations: Lec – lecanemab; PET – positron emission tomography; SE – standard error.
Amyloid status was based on amyloid PET using Centiloids. Amyloid PET using Centiloids ≥30 is considered as amyloid positive. Only patients who enrolled in the amyloid PET substudy and were amyloid positive at baseline were included.

Amyloid PET substudy

In the amyloid PET substudy (for MMRM analysis: placebo 344 patients; lecanemab 354 patients), treatment with lecanemab demonstrated a highly statistically significant reduction in amyloid plaque burden at all timepoints, with a significant reduction appearing as early as three months (p<0.00001). At all subsequent timepoints including at 18 months, lecanemab demonstrated a highly statistically significant adjusted mean change in Centiloids compared to placebo (-55.5 and 3.6 for lecanemab and placebo, respectively [adjusted mean treatment difference: -59.1; p<0.00001], Figure 15 and Table 64, Appendix O1.6). The changes from baseline compared to placebo also increased at each timepoint.

Figure 15: Adjusted mean (±SE) of change from baseline in amyloid PET using Centiloids at interim timepoints – amyloid PET PD analysis set



	Baseline	Week 13	Week 27	Week 53	Week 79
Placebo	344	303	286	259	205
Lec 10 mg/kg Biweekly	354	296	275	276	210

Source: Figure 5, Clarity AD CSR[135]
***** p<0.00001.
Abbreviations: AD – Alzheimer's disease, *APOE4* – apolipoprotein E4, MMRM – mixed model for repeated measures, PD – pharmacodynamic, PET – positron emission tomography; SE – standard error.

In addition to amyloid, Clarity AD assessed the impact of lecanemab on an extensive range of additional biomarkers in line with the AT(N) biomarker profile, with 'A' denoting amyloid, 'T' aggregated Tau, and 'N' neurodegeneration.[28] Treatment with lecanemab led to normalisation of Aβ42/40 and CSF Aβ42. Lecanemab demonstrated a reduction in plasma p-tau181, CSF p-tau181, and a reduction of neurofibrillary tangle spread on tau PET in three composite regions known to accumulate Tau early in the course of AD (temporal, medial temporal, and meta-temporal). Lecanemab also demonstrated a reduction in CSF t-Tau, CSF neurogranin, and plasma GFAP. Full biomarker results can be found in Appendix O.

B.2.6.2.3 ADAS-Cog14

ADAS-Cog14 is a scale that directly measures how a patient thinks and feels and consists of 14 tasks that include both patient-completed tests and observer-based assessments that assess memory, language, and praxis (Table 9). An delay in decline on the ADAS-Cog14 reflects, amongst other elements, improvements executive function, spoken language ability, and comprehension, which can prolong independence for patients and maintain quality of life.[141,173]

The adjusted mean difference for lecanemab compared to placebo at 18 months (-1.442) was highly statistically significant, equating to 25.8% less decline in ADAS-Cog14 (p=0.00065) (Table 18). Starting as early as six months, lecanemab showed statistically significant (p<0.05) changes from baseline compared to placebo (Figure

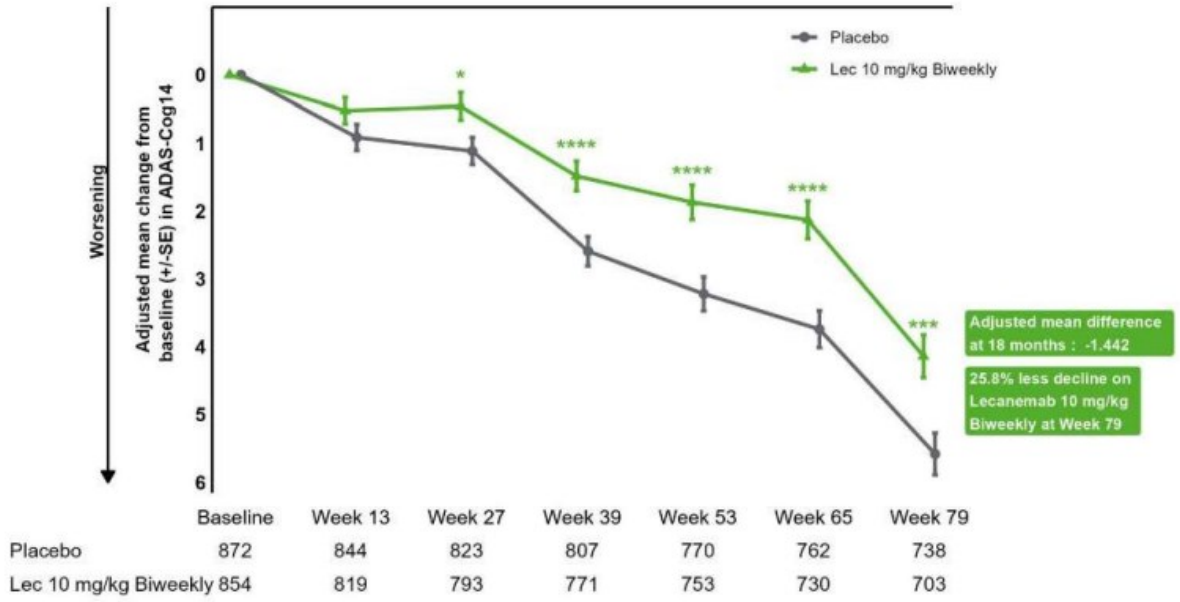
16) and at all subsequent timepoints, these changes were highly statistically significant (p<0.0001). The changes from baseline compared to placebo also tended to increase over time. Analysis of each ADAS-Cog14 item showed that the adjusted mean difference numerically favoured lecanemab over placebo across all items except constructional praxis (this test assesses the patient's ability to copy four geometric forms ranging from a very simple one [circle] to a fairly difficult one [cube]) (Figure 17).

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

Statistic	Lecanemab (n=859)	Placebo (n=875)
Number of patients included in the MMRM	854	872
N (Week 79)	703	738
Adjusted mean change from baseline (SE)	4.140 (0.314)	5.581 (0.309)
Adjusted mean difference (lecanemab – placebo)	-1.442	
95% CI for differences	-2.270, -0.613	
p-value	0.00065	
% Difference vs. placebo	-25.8%	

Source: Table 14.2.2.2.2, Clarity AD CSR[135]
Abbreviations: ADAS-Cog14 – Alzheimer's Disease Assessment Scale – Cognitive subscale 14-item version; CI – Confidence interval; FAS – Full Analysis Set; ITT – intent-to-treat; MMRM – mixed model for repeated measures; N – number of patients at each visit; n – number of patients in treatment group; SE – standard error.

Figure 16: Change from baseline in ADAS-Cog14 at interim timepoints ITT FAS+



Source: Figure 6, Clarity AD CSR[135]
* p<0.05, ** p<0.01, *** p<0.001, **** p<0.0001, ***** p<0.00001.
Abbreviations: AD – Alzheimer's disease; *APOE4* – apolipoprotein E4; ADAS-Cog14 – Alzheimer's Disease Assessment Scale – Cognitive Subscale 14-item version; FAS – Full Analysis Set; ITT – intent-to-treat; kg – kilogram; Lec – Lecanemab; mg – milligram; MMRM – mixed model for repeated measures.

Figure 17: Adjusted mean difference versus placebo in ADAS-Cog14 by item – ITT FAS+

Abbreviations: ADAS-Cog14 – Alzheimer's Disease Assessment Scale – Cognitive Subscale 14-item version; CI – confidence interval; FAS+ – Full Analysis Set; ITT – intent-to-treat.

B.2.6.2.4 ADCOMS

Alzheimer's Disease Composite Score is a composite clinical outcome consisting of four ADAS-Cog subscale items (described further in Section B.2.3.1.1), two mini mental state examination (MMSE) items, and six CDR-SB items (described further in Section B.2.3.1.1). ADCOMS is sensitive in capturing meaningful clinical decline that is characteristic of and specific to early AD, and is important to patients since it measures multiple cognitive domains, allowing for a comprehensive assessment of different aspects of cognitive function, including word recall, orientation to time, community affairs, and personal care.[143] ADCOMS can also facilitate communication between clinicians, patients, and their caregivers, since it provides a quantifiable measure of cognitive impairment, making it easier to explain the progression of the disease and its impact on daily life in a more comprehensive way than via the individual measures.[143] See Section B.2.3.1.1 for a full description.

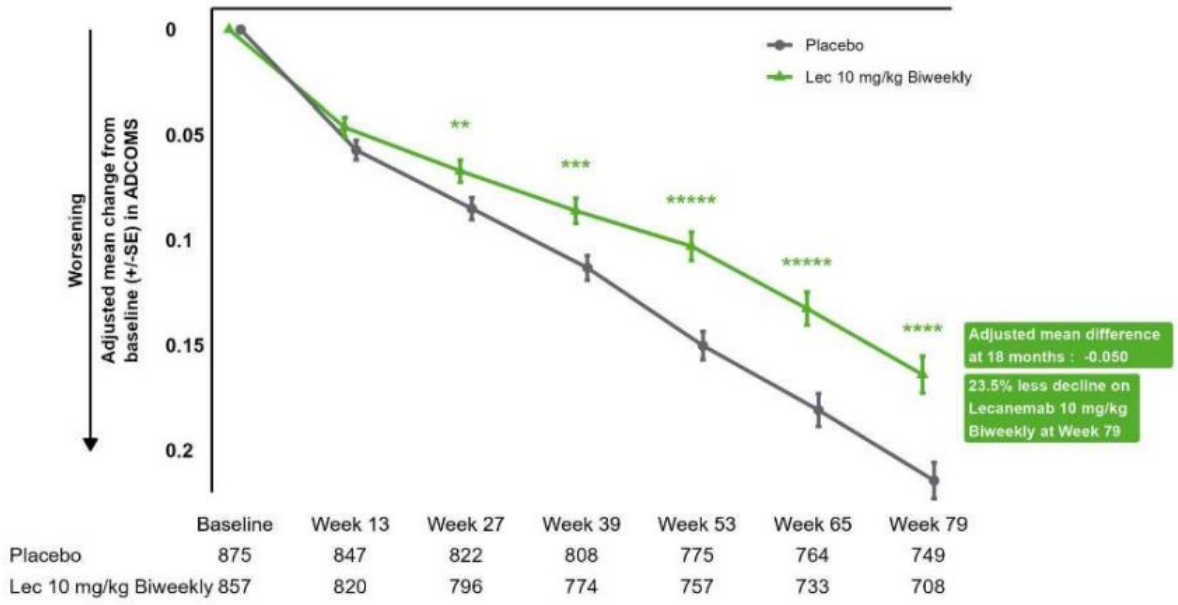
The adjusted mean difference for lecanemab compared to placebo at 18 months (-0.05) was highly statistically significant on change from baseline ADCOMS, equating to 23.5% less decline (p=0.00002) (Table 19 and Figure 18). A statistically significant difference (p<0.05) was observed as early as 6 months from baseline, becoming highly statically significant (p<0.001) from 12 months onwards. The adjusted mean difference also increased over time.

Table 19: Statistical analysis of change from baseline in ADCOMS – MMRM, ITT FAS+ – week 79

Statistic	Lecanemab (n=859)	Placebo (n=875)
Number of patients included in the MMRM	857	875
N (Week 79)	708	749
Adjusted mean change from baseline (SE)	0.164 (0.009)	0.214 (0.009)
Adjusted mean difference (lecanemab – placebo)	-0.050	
95% CI for differences	-0.074, -0.027	
p-value	0.00002	
% Difference vs. placebo	-23.5%	

Source: Table 14.2.2.3.2, Clarity AD CSR[135]
Abbreviations: ADCOMS – Alzheimer's Disease Composite Score, CI – Confidence interval; FAS – Full Analysis Set; ITT – intent-to-treat; MMRM – mixed model for repeated measures; N – number of patients at each visit; n – number of patients in treatment group; SE – standard error.

Figure 18: Change from baseline in ADCOMS – ITT FAS+



Source: Figure 7, Clarity AD CSR[135]
** p<0.01, *** p<0.001, **** p<0.0001, ***** p<0.00001.
Abbreviations: AD – Alzheimer's disease; *APOE4* – apolipoprotein E4; ADCOMS – Alzheimer's Disease Composite Score; FAS – Full Analysis Set; ITT – intent-to-treat; kg – kilogram; Lec – Lecanemab; mg – milligram; MMRM – mixed model for repeated measures.

B.2.6.2.5 ADCS MCI-ADL

ADCS MCI-ADL is a scale that directly measures how a patient functions (Section B.2.3.1.1), consisting of 18 items designed to assess IADLs such as balancing a chequebook, shopping, navigating outside the home, or finding personal belongings. Maintenance of IADLs are crucial for patients as they enable them to remain independent for an extended period, whilst also reducing the caregiving responsibilities and burdens on their caregivers.

The adjusted mean treatment difference for lecanemab compared to placebo at 18 months (2.016) was highly statistically significant, equating to 36.6% less decline in ADCS MCI-ADL (p<0.00001) (Table 20). At six months, the earliest assessment timepoint, lecanemab showed statistically significant changes (p<0.01) in ADCS MCI-ADL from baseline compared to placebo (Figure 19). At 12 and 18 months, lecanemab showed highly statistically significant changes in ADCS MCI-ADL from baseline compared to placebo (both p<0.00001). The changes from baseline compared to placebo tended to increase over time for the duration of the study.

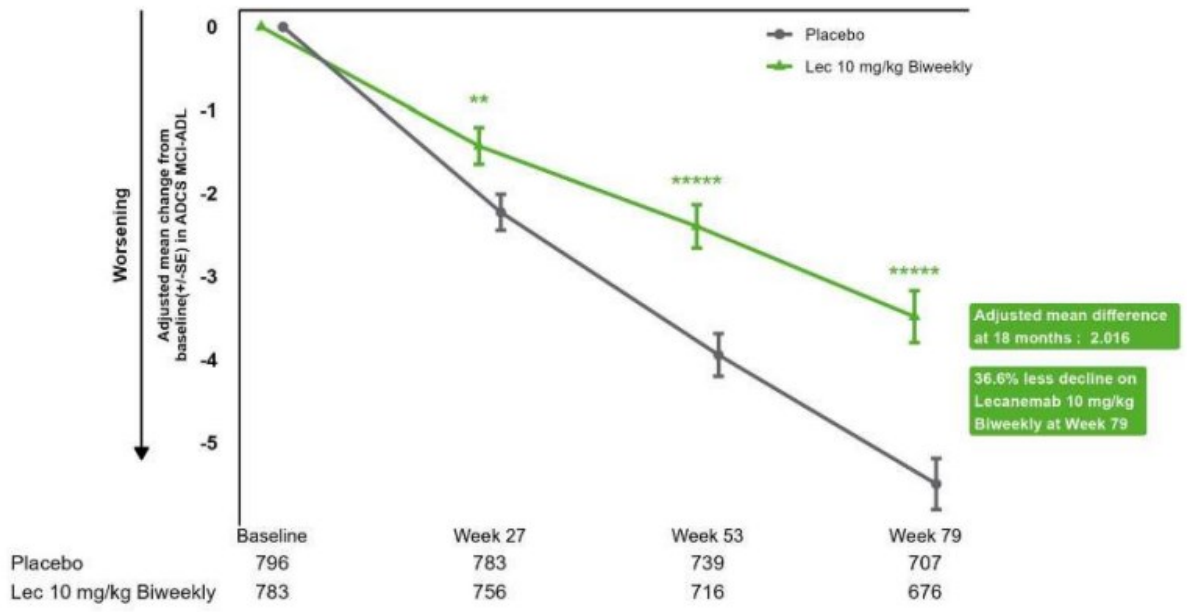
Analysis of each ADCS MCI-ADL item showed that the adjusted mean difference numerically favoured lecanemab over placebo across all items and was statistically significant for most items (Figure 20).

Table 20: Statistical analysis of change from baseline in ADCS MCI-ADL at 18 months – MMRM, ITT FAS+

Statistic	Lecanemab (n=859)	Placebo (n=875)
Number of patients included in the MMRM	783	796
N (Week 79)	676	707
Adjusted mean change from baseline (SE)	-3.484 (0.313)	-5.500 (0.308)
Adjusted mean difference (lecanemab – placebo)	2.016	
95% CI for differences	1.208, 2.823	
p-value	<0.00001	
% Difference vs. placebo	-36.6%	

Source: Table 14.2.2.4.2, Clarity AD CSR[135]
Abbreviations: ADCS MCI-ADL – Alzheimer's Disease Cooperative Study-Activities of Daily Living Scale for Mild Cognitive Impairment; CI – Confidence interval; FAS – Full Analysis Set; ITT – intent-to-treat; MMRM – mixed model for repeated measures; N – number of patients at each visit; n – number of patients in treatment group; SE – standard error.

Figure 19: Change from baseline in ADCS MCI-ADL at interim timepoints – ITT FAS+



Source: Figure 8, Clarity AD CSR[135]
** p<0.01, ***** p<0.00001.
Abbreviations: AD – Alzheimer's disease; *APOE4* – apolipoprotein E4; ADCS MCI-ADL – Alzheimer's Disease Cooperative Study-Activities of Daily Living Scale for Mild Cognitive Impairment; FAS – Full Analysis Set; ITT – intent-to-treat; kg – kilogram; Lec – Lecanemab; mg – milligram; MMRM – mixed model for repeated measures.

Figure 20: Adjusted mean difference versus placebo in ADCS MCI-ADL by item – ITT FAS+

Abbreviations: ADCS MCI-ADL – Alzheimer's Disease Cooperative Study-Activities of Daily Living Scale for Mild Cognitive Impairment; FAS – Full Analysis Set; ITT – intent-to-treat; MMRM – mixed model for repeated measures.

B.2.6.3 Relationship between amyloid PET and CDR-SB

As detailed in Section B.2.6.2.1, a reduction in amyloid was observed in Clarity AD. Lecanemab was shown to slow progression of AD as measured by CDR-SB (see Section B.2.6.1). Amyloid reduction provides pathophysiological support underlying the clinical efficacy findings in CDR-SB. Lecanemab targets highly toxic protofibrils, prior to their evolution into amyloid plaques, as well as amyloid plaques themselves, resulting in rapid reduction of amyloid PET levels.. This is reflected in a slowing of decline as measured by CDR-SB. A correlation analysis was conducted to determine the link between amyloid load and CDR-SB. There was a patient-level correlation between the amount of amyloid removal as measured on amyloid PET (Centiloids) and CDR-SB (Figure 21, Pearson correlation coefficient=0.45, p<0.0001). This correlation demonstrates that the effect of lecanemab on amyloid is correlated with the effect of lecanemab on CDR-SB. The correlation between the biomarker change and the slowing of disease progression is correlated in a causal way. Mediation analyses conducted to explore the relationship between the effect of lecanemab on CDR-SB showed 80% of the effect on CDR-SB can be explained by reduction in amyloid PET (Centiloids), therefore providing reliable evidence of biomarker change as a surrogate endpoint for a clinical efficacy measure (full results presented in Appendix O1.5).[138,174]

Figure 21: Linear trend between reduction in amyloid PET (Centiloids) and slowing of decline on CDR-SB

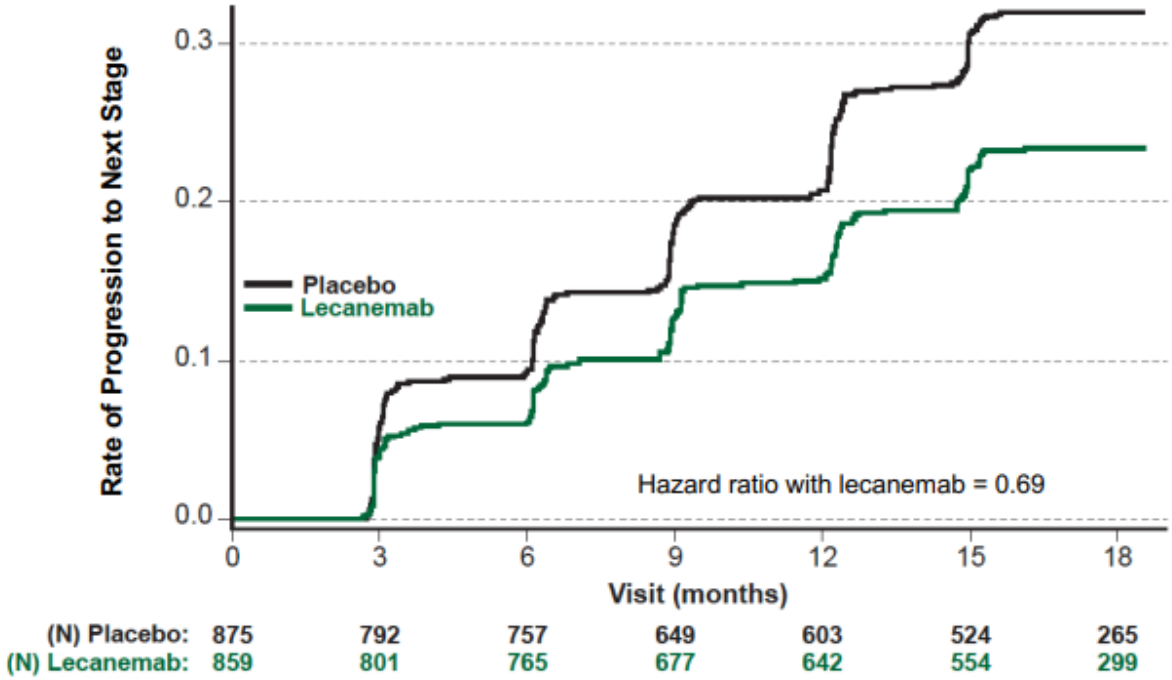
Abbreviations: CDR-SB – Clinical Dementia Rating–Sum of Boxes; PET – positron emission tomography.

B.2.6.4 Key exploratory endpoint: Time to worsening of Global CDR score at 18 months

Time to worsening of global CDR score was defined as time from randomisation to worsening of the global CDR score (i.e., the first increase from baseline by at least

0.5 points on the global CDR score in two consecutive visits). In the lecanemab group, [redacted]% of patients had experienced a worsening of global CDR at three months, increasing to only [redacted]% at 18 months. In comparison, [redacted]% of patients in the placebo group had experienced a worsening of global CDR at three months, increasing to [redacted]% at 18 months (Appendix O1.3). At 18 months, lecanemab showed a statistically significant reduction in the risk of progression to the next stage of AD on the global CDR score by 31% (hazard ratio = 0.69, 95% CI 0.57-0.83, *p*=0.00011) (Figure 22). This delay in progression to more severe AD health states means that patients receiving lecanemab remain at home in their community and independent when completing ADLs for longer, which may delay or reduce residential care placement.[175]

Figure 22: Time to worsening Global CDR Score



Source : van Dyck et al.[3]
Abbreviations: CDR – Clinical Dementia Rating.

B.2.6.5 Exploratory endpoints – Health-related quality of life

HRQoL assessments provide a unique insight and perspective from the patient with respect to their own perceptions of how the disease affects them, encompassing mental, physical, and social aspects of life.[176] They provide a perception of how a patient's wellbeing is affected by disease and are ideally rated by patients in relation to their personal expectations, which can vary over time.[176] Caregivers are faced with substantial burden when caring for loved ones with AD, and the severity of burden increases significantly as the disease progresses (see Section B.1.3.4.2 for further detail). A unique and positive feature of Clarity AD was the collection of three types of HRQoL data which allowed direct measurement of how lecanemab

treatment impacted patients and their carers (Table 8): Patient's Survey – patient's own assessment of HRQoL; Partner as a Proxy Survey – study partner's assessment of patient HRQoL; and Partner's Survey – study partner's assessment of their own HRQoL. These were measured at baseline and every six months up to 18 months.

In early AD, proxy QoL measurements are necessary and reasonable when patients reach stages of AD where worsening cognitive function limits a patient's insight into their own QoL and/or their ability to communicate their QoL. Three QoL instruments were used in Clarity AD: EQ-5D-5L, QOL-AD, and ZBI.

EQ-5D-5L measures five dimensions of health (mobility, self-care, pain/discomfort, usual activities, and anxiety/depression) with five levels of severity in each dimension (no problems, slight problems, moderate problems, severe problems, and extreme problems).[145] The VAS score measures the self-assessed health status of the respondent on a graduated scale from 0 to 100, where higher scores correspond to a greater level of HRQoL. EQ-5D-5L can be completed by the patient, study partner as a proxy, and study partner. The advantages of using the EQ-5D-5L scale are that it is very widely used, meaning it is generalisable and comparable between studies and disease areas; has increased sensitivity compared to its predecessor, the EQ-5D-3L scale; has well-established validity and reliability; and is widely used in economic evaluations.[177] All EQ-5D-5L results are reported in Section B.2.6.5.1.

QOL-AD is a 13-item questionnaire with a four-point scale to rate a variety of life domains, including the patient's physical health, mood, relationships, and ability to complete tasks.[146,147] Responses range from 1-4 (poor, fair, good, excellent) and each item is summed to give a total score of 13–52, with higher scores indicating better QoL. QOL-AD can be completed by the patient or study partner as a proxy. QOL-AD is a disease-specific QoL instrument and has therefore been designed specifically with patients with cognitive impairment in mind, using feedback from AD patients, caregivers and experts in the field.[146,147] It is therefore considered to be more sensitive than EQ-5D-5L when assessing QoL in AD patients.

ZBI is a 22-item instrument where each item on the interview is a statement which the caregiver is asked to endorse using a five-point scale.[148] Response options range from 0 (never) to 4 (always). Scores are summed to give a total score out of 88. The total score range is 0-88 (0-21: no to mild burden; 21-40: mild to moderate burden; 41-60: moderate to severe burden; 61-88: severe burden) and the ZBI is completed solely by the study partner. These endpoints are described further in Section B.2.3.1.1.

Lecanemab was associated with a relative preservation of HRQoL and less worsening of caregiver burden. Consistent benefits were seen across different scales, within scales, and across randomisation strata. There were statistically significant differences between placebo and lecanemab at 18 months in most

assessments of patient QoL (patient-reported EQ-5D-5L and QOL-AD; patient-by-proxy QOL-AD) as well as for caregiver burden (ZBI). Adherence across all endpoints for patients, patient-by-proxy, and study partners remained consistently above [redacted]%. Results by domain were generally consistent with the overall results for each instrument and were generally in favour of lecanemab. All but two of the 18 domains of QOL-AD favoured lecanemab in the Patient's Survey and all 18 domains favoured lecanemab in the patient-by-proxy survey. In the ZBI questionnaire, all items favoured lecanemab.

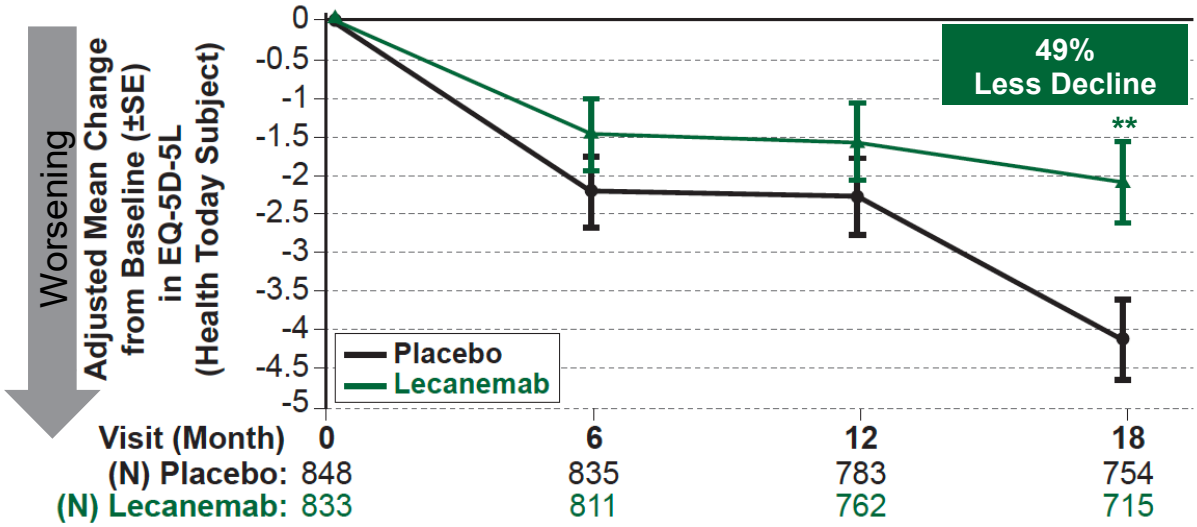
B.2.6.5.1 EQ-5D-5L

B.2.6.5.1.1 Patient-reported

The Health Today VAS records the respondent's self-rated health status on a graduated (0–100) scale, with higher scores for higher HRQoL. The adjusted mean difference for lecanemab compared to placebo in the Patient's Survey at 18 months (2.017) was highly statistically significant, representing 49.1% less decline (p=0.00383 [Figure 23]). Figure 24 presents results by dimension, with lecanemab favoured in the self-care dimension and statistically favoured in the anxiety/depression and usual activities dimensions. For the mobility and pain/discomfort dimensions, the placebo group improved versus baseline, so the "percent less decline" represents percentage less improvement. It should be noted that lecanemab was favoured in the three most relevant domains, anxiety/depression, self-care, and usual activities. Mobility and pain/discomfort are not as clinically relevant to patients with early AD.

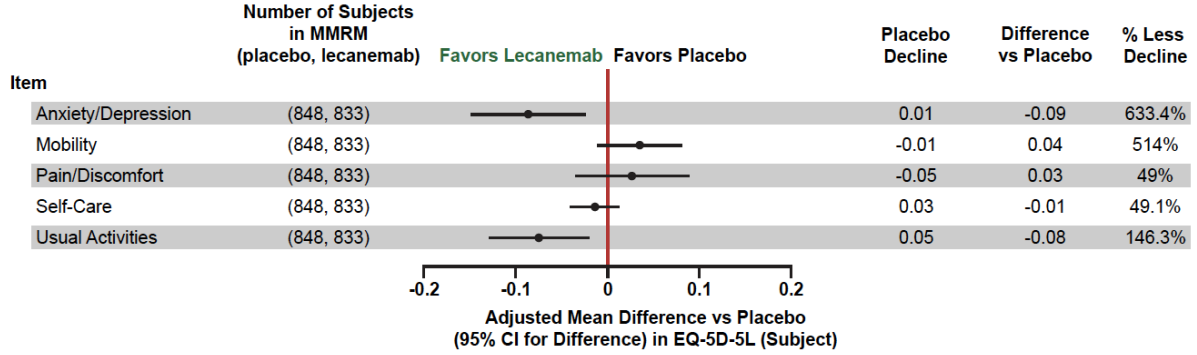
These results show that patients receiving lecanemab experience significantly less decline in their quality of life compared to placebo when assessed through the patient survey. The absolute difference between arms increased at each assessment timepoint. As AD progresses, patients face challenges in accurately assessing their own QoL. Therefore, preservation of QoL during the early stages of the disease is especially significant. At the early AD phase, patients often retain the ability to carry out most of their daily activities and maintain a lifestyle similar to that which they had before the disease progressed significantly.

Figure 23: Adjusted mean change from baseline in EQ-5D-5L, Health today (VAS subtotal), patient-reported



Source : Cohen et al. 2023[178]
** $p<0.01$.
Abbreviations : SE – standard error.

Figure 24: Adjusted mean change from baseline in EQ-5D-5L by domain, Health today (VAS subtotal) at 18 months, patient-reported



Source : Cohen et al. 2023[178]
Abbreviations: CI – confidence interval; MMRM – mixed model for repeated measures.

B.2.6.5.1.2 Partner as a Proxy

The adjusted mean difference for lecanemab compared to placebo in the Partner as a Proxy Survey at 18 months ([redacted]) equated to [redacted]% less decline, [redacted] (Table 21).

Table 21: Statistical analysis of change from baseline in EQ-5D-5L, Health today (VAS subtotal) at 18 months, Partner as a Proxy – MMRM, ITT FAS+

Statistic	Lecanemab (n=859)	Placebo (n=875)
Number of patients included in the MMRM	[redacted]	[redacted]
N (Week 79), (%)	[redacted]	[redacted]

Adjusted mean change from baseline (SE)	[redacted]	[redacted]
Adjusted mean difference (lecanemab – placebo)	[redacted]	
95% CI for differences	[redacted]	
p-value	[redacted]	
% Difference vs. placebo	[redacted]	

Source: Table 14.2.3.4.2, Clarity AD CSR[135]
Abbreviations: CI – Confidence interval;; FAS – Full Analysis Set; ITT – intent-to-treat; MMRM – mixed model for repeated measures; n – number of patients in treatment group; N – number of patients at each visit; SE – standard error.

B.2.6.5.1.3 *Study partner*

The adjusted mean difference for lecanemab compared to placebo in the Partner's Survey ([redacted]) represented [redacted]% more decline, [redacted] (Table 22).

Table 22: Statistical analysis of change from baseline in EQ-5D-5L, Health today (VAS subtotal) at 18 months, Study partner – MMRM, ITT FAS+

Statistic	Lecanemab (n=859)	Placebo (n=875)
Number of patients included in the MMRM	[redacted]	[redacted]
N (Week 79), (%)	[redacted]	[redacted]
Adjusted mean change from baseline (SE)	[redacted]	[redacted]
Adjusted mean difference (lecanemab – placebo)	[redacted]	
95% CI for differences	[redacted]	
p-value	[redacted]	
% Difference vs. placebo	[redacted]	

Source: Table 14.2.3.4.2, Clarity AD CSR[135]
Abbreviations: CI – confidence interval; FAS – Full Analysis Set; ITT – intent-to-treat; MMRM – mixed model for repeated measures; n – number of patients in treatment group; N – number of patients at each visit; SE – standard error.

B.2.6.5.1.4 *Utility scores*

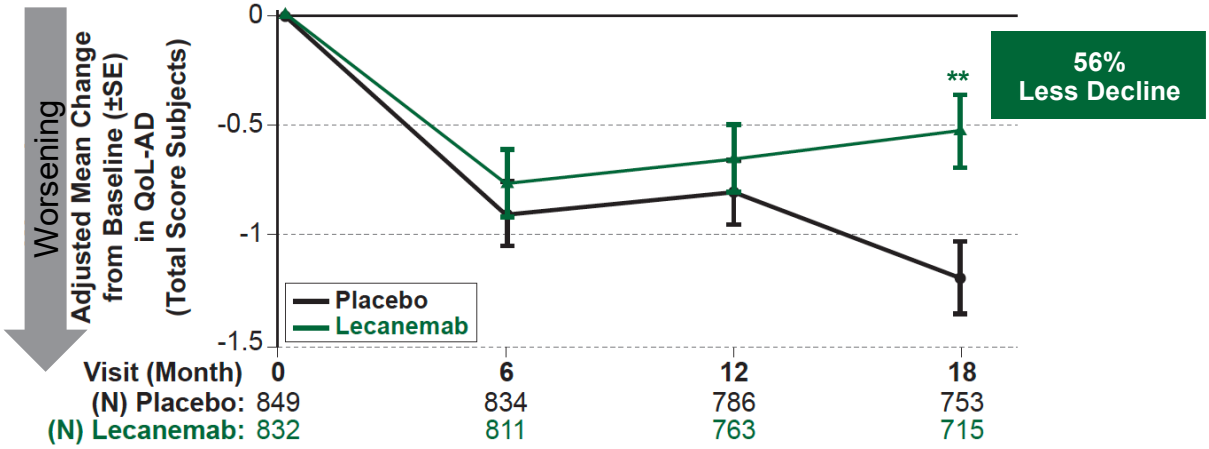
EQ-5D-5L scores for lecanemab and placebo were measured at six, 12, and 18 months and were converted to utility scores, full results of which are provided in Appendix O1.9. Lecanemab utility scores were consistently higher than the placebo utility scores across all timepoints and change from baseline was lower for lecanemab compared to placebo in almost all instances, excluding two instances in the study partner utility score. Although no minimal clinically important difference (MCID) has been established for EQ-5D-5L in AD, MCIDs have been assessed for EQ-5D, with values reported in the range 0.03-0.52 and an average of 0.18.[179,180]

B.2.6.5.2 QOL-AD

B.2.6.5.2.1 *Patient-reported*

The adjusted mean difference for lecanemab compared to placebo in the Patient's Survey at 18 months (0.657) was highly statistically significant, equating to 55.6% less decline (p=0.00231). While both lecanemab and placebo showed initial decline in QOL-AD at six months, lecanemab demonstrated improvement in QOL-AD at 12 and 18 months relative to the six-month assessment (Figure 25). The effect of lecanemab was consistent across 11 of 13 QOL-AD domains (Figure 26), including less decline in the 'ability to do chores' (51.8%), 'ability to do things' (40.2%), 'friends' (57.6%), and 'life as a whole' (66.1%).

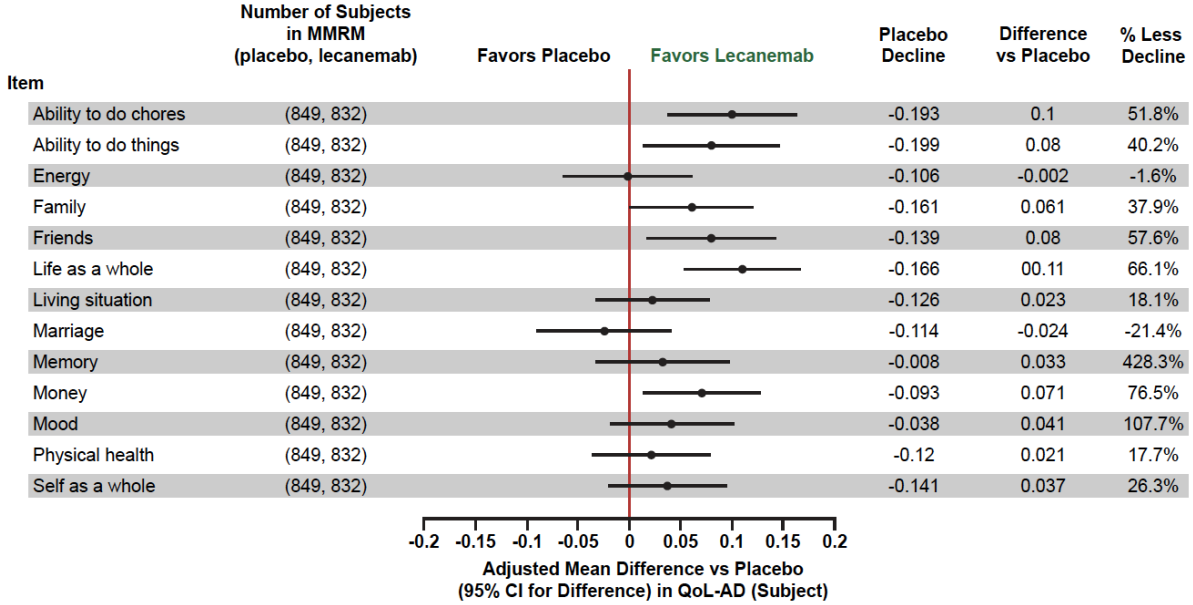
Figure 25: Adjusted mean change from baseline in QOL-AD, patient-reported



Source : Cohen et al. 2023[178]

Abbreviations: QOL-AD – Quality of life in Alzheimer's Disease; SE – standard error.

Figure 26: Adjusted mean change from baseline in QOL-AD by item at 18 months, patient-reported

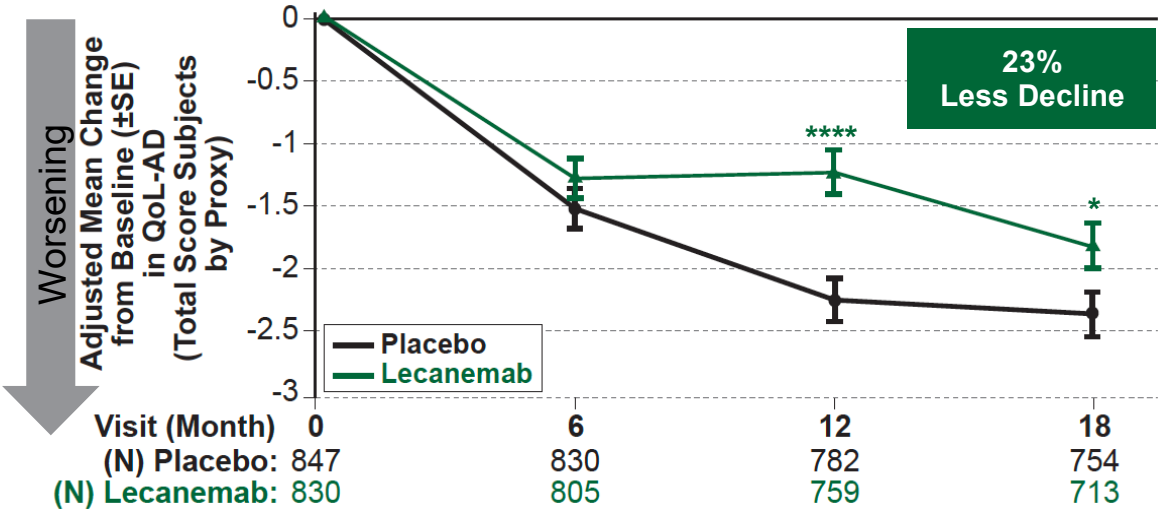


Source : Cohen et al. 2023[178]
Abbreviations: CI – confidence interval; MMRM – mixed model for repeated measures; QOL-AD – Quality of life in Alzheimer's Disease.

B.2.6.5.2.2 *Partner as a Proxy*

The adjusted mean difference between lecanemab and placebo in the Partner as a Proxy Survey at 18 months (0.535) was statistically significant, equating to 22.9% less decline, *p*=0.02558 (Figure 27), consistent with the patient-reported results for QOL-AD. The effect for lecanemab was consistent across all QOL-AD domains (Figure 28).

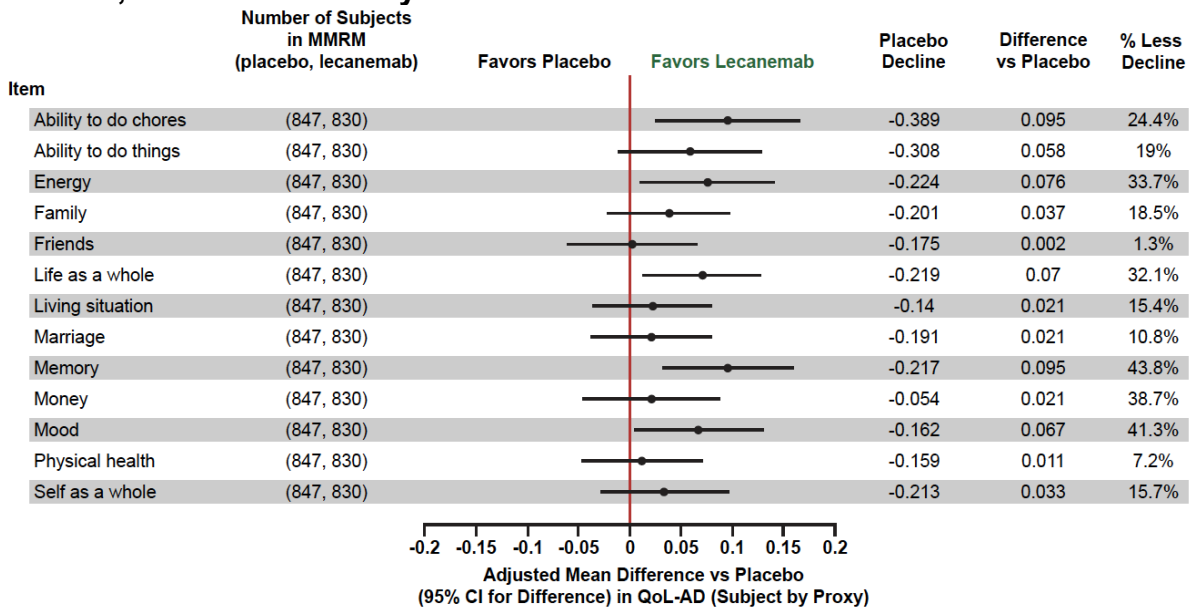
Figure 27: Adjusted mean change from baseline in QOL-AD, Partner as a Proxy



Source : Cohen et al. 2023[178]

Abbreviations: QOL-AD – Quality of life in Alzheimer's Disease; SE – standard error.

Figure 28: Adjusted mean change from baseline in QOL-AD by item at 18 months, Partner as a Proxy



Source : Cohen et al. 2023[178]

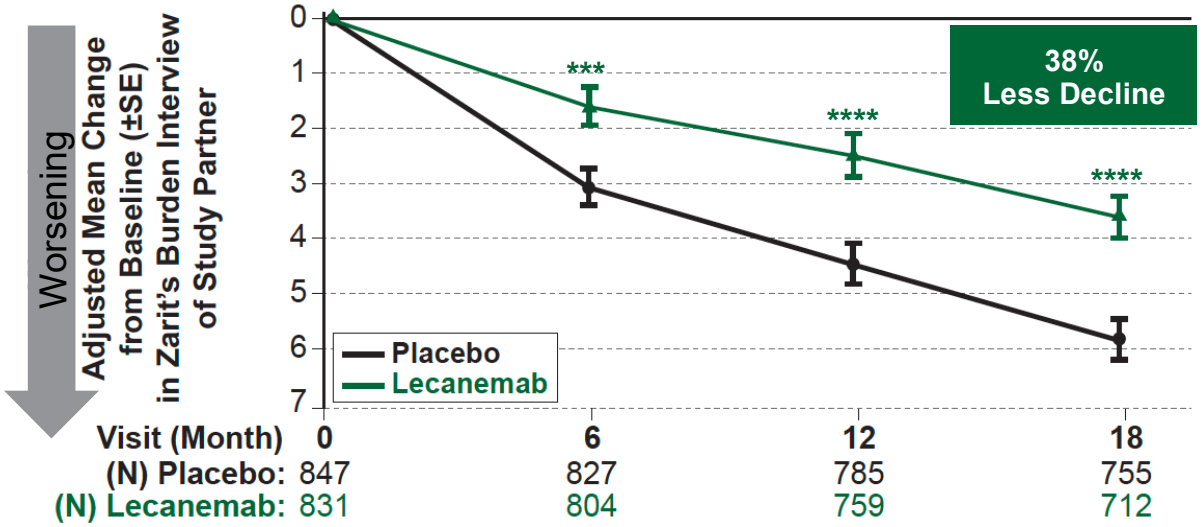
Abbreviations: CI – confidence interval; MMRM – mixed model for repeated measures; QOL-AD – Quality of life in Alzheimer's Disease.

Both the patient-reported and partner as a proxy QOL-AD measurements displayed highly statistically significant differences between lecanemab and placebo at 18 months, indicating that patients receiving lecanemab experienced a substantially smaller decline in their QoL compared to those who received placebo. This finding has meaningful implications for patients with AD as it indicates lecanemab could help them maintain a more fulfilling life through the potential slowing of disease progression. It may also alleviate some of the caregiving burden on families as patients may require less intensive care if their QoL remains higher for longer, as demonstrated in a recent meta-analysis.[181]

B.2.6.5.3 Zarit's Burden Interview

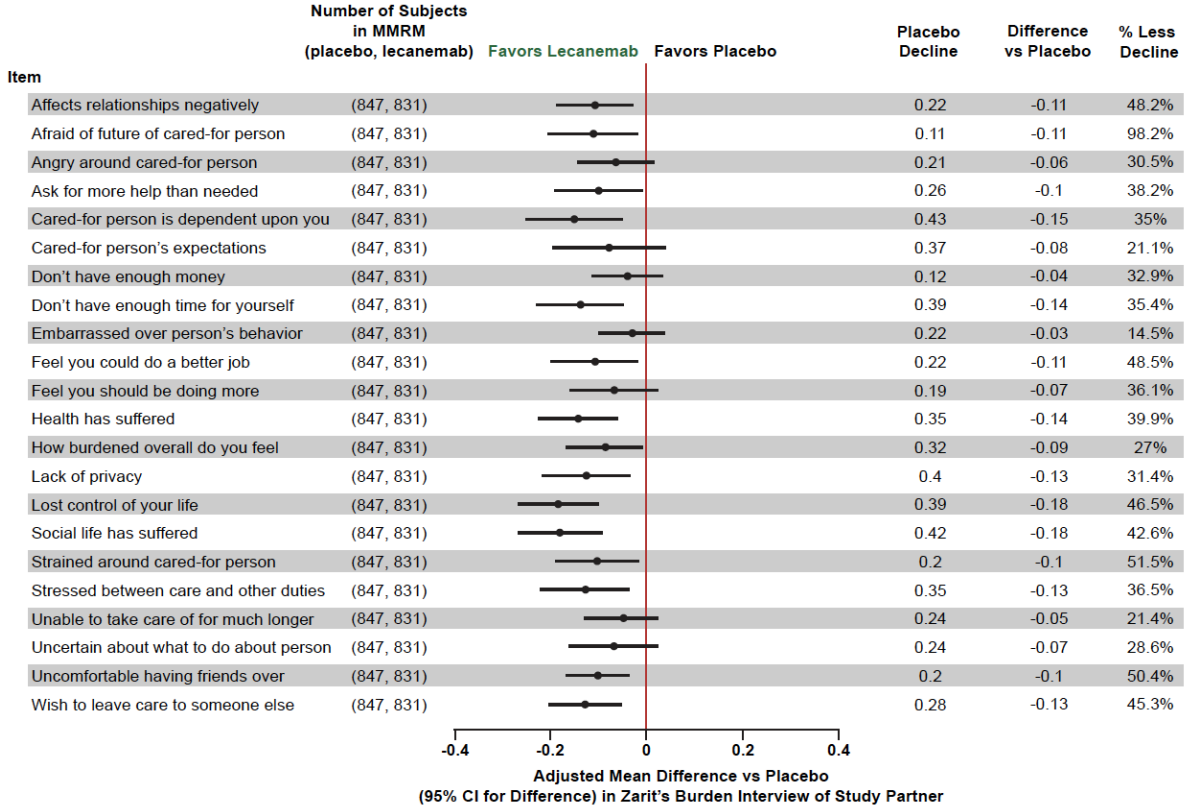
The adjusted mean difference between lecanemab compared to placebo at 18 months (-2.211) was highly statistically significant, equating to 38.4% less decline, *p*=0.00002 (Figure 29). This effect was consistent across all 22 domains (Figure 30). This shows that lecanemab addresses common caregiver concerns, such as not having enough time, money, or privacy, or feeling as if one's relationships and social life have suffered. A 38.4% reduction in decline suggests that lecanemab treatment can alleviate a portion of the caregiving burden for carers of patients with AD. This can lead to improved mental and emotional health of carers, reduced caregiver burnout, and enhanced family dynamics.[181]

Figure 29: Adjusted mean change from baseline in ZBI



Source : Cohen et al. 2023[178]
Abbreviations: SE – standard error.

Figure 30: Adjusted mean change from baseline in ZBI by item at 18 months



Source : Cohen et al. 2023[178]
Abbreviations: CI – confidence interval; MMRM – mixed model for repeated measures.

B.2.6.5.4 QoL summary

Deterioration in QoL and worsening care partner burden are key aspects of the progression of AD. This worsening can be detected in early AD and was quantified over the 18-month timeframe of Clarity AD. Lecanemab was associated with a greater relative preservation of QoL, and reduction in caregiver burden compared to placebo, as reported by patients and their study partners, with consistent benefits seen across different scales, within items, and within the vast majority of subdomains of these scales.

The concept of "meaningful benefits" to AD patients is based on a comprehensive incorporation of cognition, function, quality of life, and caregiver burden, and includes advantages like buying more time for patients in less severe stages of disease and preserving QoL.[182,183] The clinical and QoL benefits seen in Clarity AD may lead to a cumulative long-term cumulative advantage, where the gap between benefits on and off treatment may continue to grow over time, extending beyond what was observed in the 18-month trial period.[3,159]

The adjusted mean change from baseline in EQ-5D-5L showed 49% less decline as reported by patients and 7% less decline based on the proxy survey at 18 months in patients treated with lecanemab. The adjusted mean change from baseline at 18 months in QOL-AD by patient showed 56% less decline, compared with 23% less

decline in the proxy survey. Study partner burden measured by Zarit Burden Interview also resulted in 38% less decline at 18 months.

A recent meta-analysis demonstrated that patient's self-reported QoL is correlated with carer's QoL, whilst another study showed a link between carer burden and carer QoL.[181,184] If carer burden is reduced, this frees up their time to maintain their usual relationship with the AD patient. It was hypothesised that improvements in carer burden should therefore indirectly improve patient's QoL, indicating the importance of improving outcomes for both patient and carer.

The consistency of results across similar individual items and domains of the QoL instruments provides strong additional evidence for relevant benefits to both lecanemab patients and their care partners, beyond any clinical benefits demonstrated through changes in biomarkers, and cognitive and functional measures. Greater relative preservation of patient's self-reported QoL is of particular importance in early AD when patients are aware of their wellbeing and autonomy, as opposed to later stages of AD when they may be unaware of their decline due to loss of cognition.

B.2.7 Subgroup analysis

B.2.7.1 Pre-specified subgroup analyses

The primary endpoint, key secondary endpoints, and biomarker endpoints in Clarity AD were analysed by a range of pre-specified subgroups according to randomisation strata and intrinsic factors (Table **23**). Statistical analysis was performed as per the analysis on the overall population, using the same MMRM without imputed data, as described in Section B.2.4.2. Clinical subgroup and *APOE4* carrier status were also pre-specified in the final scope of this submission. Randomisation strata subgroups were chosen based on the overall study design and these represent covariates of interest in Clarity AD. The intrinsic factor subgroups were identified as other variables of interest, but these were not influenced by study design.

Table 23: Pre-specified subgroup analyses in Clarity AD

Subgroup	Categories
Randomisation strata	
Use of symptomatic AD medication at baseline	Yes; no
Clinical subgroup	MCI; mild AD
APOE4 carrier	Noncarrier; carrier
Region	North America; Asia; Europe
Intrinsic factors	
APOE4 genotype status	Noncarrier; heterozygote; homozygote
Sex	Female; male
Age	<65; 65-74; ≥75
Ethnicity – Global	Hispanic; Non-Hispanic

Race – Global	White; Asian; Black
Ethnicity – United States	Hispanic; Non-Hispanic
Race – United States	White; Black

Abbreviations: AD – Alzheimer's disease; *APOE4* – apolipoprotein E4; MCI – mild cognitive impairment.

The results of analyses for these subgroups are presented in Appendix E. Clarity AD was not powered for individual subgroups; hence the results of subgroup analyses are hypothesis-generating only and must be interpreted in the context of variability, sample size, and placebo decline.

B.2.7.2 Post-hoc subgroup analyses

In addition to the pre-specific subgroup analyses, a post-hoc analysis was conducted to evaluate antithrombotic (antiplatelet and anticoagulant) treatment use in patients who experienced ARIA in Clarity AD. Results are described in Appendix E.

B.2.8 Meta-analysis

A meta-analysis of Clarity AD and Study 201 was not conducted for this submission because:

- Clarity AD is the pivotal study supporting the marketing authorisation of lecanemab, whereas Study 201 was a Phase II dose-finding study.
- Study 201 had a different primary endpoint (ADCOMS) to Clarity AD (CDR-SB) and was not powered to detect differences between lecanemab and placebo in CDR-SB score.
- Only 161 patients in Study 201 were treated with 10 mg/kg biweekly lecanemab, of which [redacted] completed study treatment. In contrast, 898 patients were treated with 10 mg/kg biweekly lecanemab in Clarity AD and 729 patients completed the core study.

B.2.9 Indirect and mixed treatment comparisons

An indirect treatment comparison was not conducted as Clarity AD provides direct evidence for the comparison of interest.

B.2.10 Adverse reactions

Safety was assessed in Clarity AD by monitoring and recording all AEs, and by monitoring haematology, blood chemistry and urinalysis, measurement of vital signs (systolic and diastolic blood pressure [BP], pulse, respiratory rate, body temperature, and weight), electrocardiograms (ECGs), and physical examinations during the treatment period. For all AEs, a patient with two or more events was counted only once for that event. This applies throughout this section. As discussed in Section B.2.3.1.2, ARIA were monitored closely and managed according to the extent of ARIA and prior occurrence. Patients who developed both ARIA-H and ARIA-E that

resulted in study drug interruption permanently discontinued treatment if they experienced a third occurrence of either event.

Safety data from the core study period of Clarity AD are presented below. The open-label extension (OLE) study of Clarity AD, designed to evaluate the long-term safety and tolerability of lecanemab and evaluate whether the benefits of lecanemab are maintained over time, is ongoing.

B.2.10.1 Extent of exposure

Duration of exposure to treatment was calculated as the number of days between the date a patient received the first dose of lecanemab and the date they received the last dose plus one treatment cycle. The duration of a treatment cycle was two weeks. In the core study, median duration of exposure was equal at [redacted] months for both lecanemab (range: [redacted]) and placebo (range: [redacted]) (Table 24). Overall exposure (number of patient-years) was similar between lecanemab ([redacted] patient-years) and placebo ([redacted] patient-years).

Treatment was well tolerated with similar overall incidence of TEAEs and treatment-emergent serious adverse events (TESAEs) between lecanemab and placebo. Additionally, the majority of patients in both arms completed the study (lecanemab: [redacted]%; placebo: [redacted]%), with [redacted]% of lecanemab patients discontinuing from study drug due to TEAEs, compared to [redacted]% for placebo. A similar proportion of patients entered the OLE study (lecanemab: [redacted]%; placebo: [redacted]%). The median compliance rate was [redacted] in the lecanemab arm and [redacted] in the placebo arm.

Table 24: Clarity AD drug exposure, SAS

Duration of exposure (months)	Lecanemab (n=898)	Placebo (n=897)
n	898	897
Mean (SD)	[redacted]	[redacted]
Median	[redacted]	[redacted]
Min, Max	[redacted]	[redacted]
Total duration (patient-years)[a]	[redacted]	[redacted]

Source: Table 9, Clarity AD CSR[135]
Abbreviations: Max – maximum; Min – minimum; n – number of patients in treatment group; SAS – Safety Analysis Set; SD – standard deviation.
[a] Total duration (patient-years) – summation over all patients' exposure durations.

B.2.10.2 AEs overview

TEAEs were defined as an AE that emerged, re-emerged or worsened in severity relative to the pretreatment state during treatment or within 30 days following the last dose of study drug, having been absent at pretreatment. A summary of TEAEs that occurred in Clarity AD is presented in Table 25. AEs, with the exception of infusion

related reactions, were graded on a three-point scale of mild (discomfort noticed, but no disruption of normal daily activities), moderate (discomfort sufficient to reduce or affect normal daily activities) and severe (incapacitating, with inability to work or perform normal daily activities). Infusion related reactions were graded based on the Common Terminology Criteria for Adverse Events (CTCAE).[185] AEs of special interest are presented in MedDRA Preferred Terms throughout the document.

The overall incidence of TEAEs was similar between lecanemab (798/898 [88.9%]) and placebo (735/897 [81.9%]), with the most common TEAEs for patients receiving lecanemab including infusion related reactions ([redacted]%), ARIA-H (14.0%) and ARIA-E (12.6%) (Table 26). ARIA-E occurrences were monitored by early MRI and managed by dose interruption until resolution. The majority (81%) of ARIA-E cases resolving by four months since onset, with 7.9% of lecanemab and 0.7% of placebo patients experiencing interruption of study drug due to ARIA-E (Section B.2.3.1.2). Infusion related reactions were largely mild to moderate (as per CTCAE grading), associated with the first dose, and could be managed with prophylactic treatment. In the lecanemab arm, only seven (0.8%) patients experienced a severe infusion-related reaction.

The incidence of AEs leading to discontinuation of study treatment was [redacted]% and [redacted]% in the lecanemab and placebo arms, respectively (Table 68, Appendix O1.7). This difference is attributable to lower incidence of infusion related reaction (lecanemab: [redacted]%, placebo: [redacted]%), ARIA-H ([redacted]% versus [redacted]%), ARIA-E ([redacted]% versus [redacted]%), and superficial siderosis of the central nervous system ([redacted]% versus [redacted]%) in the placebo arm compared with the lecanemab arm. The incidence of TEAEs leading to study drug dose adjustment was [redacted]% and [redacted]% in the lecanemab and placebo arms, respectively. This difference was attributable to management of infusion related reactions, ARIA-E, and ARIA-H, which were more common in patients treated with lecanemab (Table 25).

Table 25: Adverse event overview (Clarity AD, SAS)

Category	Number of patients, n (%)	
	Lecanemab (n=898)	Placebo (n=897)
TEAEs	798 (88.9)	735 (81.9)
Treatment-related TEAEs[a]	401 (44.7)	197 (22.0)
Severe TEAEs	[redacted]	[redacted]
Serious TEAEs	126 (14.0)	101 (11.3)
Deaths[b]	6 (0.7)	7 (0.8)
Other SAEs[c]	[redacted]	[redacted]
Life threatening	[redacted]	[redacted]
Requires inpatient hospitalisation or prolongation of existing hospitalisation	[redacted]	[redacted]
Persistent or significant disability or incapacity	[redacted]	[redacted]
Congenital anomaly/birth defect	[redacted]	[redacted]
Important medical events	[redacted]	[redacted]
TEAEs leading to study drug dose adjustment	[redacted]	[redacted]
TEAEs leading to study drug withdrawal	[redacted]	[redacted]
TEAEs leading to study drug dose interruption	[redacted]	[redacted]
TEAEs leading to infusion interruption	[redacted]	[redacted]
TEAEs of special interest	[redacted]	[redacted]

Source: Table 10, Clarity AD CSR[135]
Abbreviations: AE – adverse event; MedDRA – Medical Dictionary for Regulatory Activities; n – number of patients in treatment group; SAE – serious adverse event; SAS – Safety Analysis Set; TEAE – treatment-emergent adverse event.
A: Includes TEAEs considered by the Investigator to be related to study drug or TEAEs with missing causality.
B: Includes all patients with SAE resulting in death.
C: Includes patients with nonfatal SAEs only. If a patient had both fatal and nonfatal SAEs, the patient is counted in the previous fatal row and is not counted in the nonfatal row.

B.2.10.3 AEs in ≥5% of patients

TEAEs of any severity occurring in ≥5% of patients in either treatment arm reported during the core study are summarised by decreasing frequency in Table 26. Excluding infusion-related reactions and ARIA, which occurred at a lower rate in

placebo than lecanemab, TEAEs occurring in ≥5% of patients were similar between lecanemab and placebo. Concurrent ARIA-E and ARIA-H, defined as overlapping in the AE duration of two ARIA events, occurred in 8.2% of lecanemab patients compared to 1.0% of placebo patients, however similar rates of isolated ARIA-H were observed between arms (lecanemab: 8.9%; placebo: 7.8%) (Section B.2.10.4.2.2). In this table, ARIA-H is separated out into (1) ARIA-H cerebral microhaemorrhage and (2) superficial siderosis.

Table 26: Treatment-emergent AEs reported in ≥5% of patients (Clarity AD, SAS)

MedDRA Preferred Term	Number of patients, n (%)	
	Lecanemab (n=898)	Placebo (n=897)
Patients with any TEAE	798 (88.9)	735 (81.9)
Infusion related reaction	[redacted]	[redacted]
ARIA-H microhaemorrhages and haemosiderin deposits	126 (14.0)	69 (7.7)
ARIA-E	113 (12.6)	15 (1.7)
Headache	100 (11.1)	73 (8.1)
Fall	93 (10.4)	86 (9.6)
Urinary tract infection	78 (8.7)	82 (9.1)
COVID-19	64 (7.1)	60 (6.7)
Back pain	60 (6.7)	52 (5.8)
Arthralgia	53 (5.9)	62 (6.9)
Superficial siderosis of central nervous system	50 (5.6)	22 (2.5)
Dizziness	49 (5.5)	46 (5.1)
Diarrhoea	48 (5.3)	58 (6.5)
Anxiety	45(5.0)	38 (4.2)

Source: Table 11, Clarity AD CSR[135]
Abbreviations: AE – adverse event; ARIA-E – amyloid-related imaging abnormality-oedema/effusion; ARIA-H – amyloid-related imaging abnormality-microhaemorrhage and haemosiderin deposit; COVID-19 – Coronavirus disease of 2019; MedDRA – Medical Dictionary for Regulatory Activities; n – number of patients in treatment group; SAS – Safety Analysis Set; TEAE – treatment-emergent adverse event

B.2.10.4 Adverse events of special interest

Infusion-related reactions, skin rash, other hypersensitivity reactions, ARIA-E, and ARIA-H occurred at a higher incidence in the lecanemab arm ([redacted]%]) than the placebo arm ([redacted]%]) (Table 27), and most were considered treatment-related (lecanemab ([redacted] placebo ([redacted] (Clarity AD CSR, Table 16.3.2.6.2). Excluding infusion-related reactions, ARIA-E, and ARIA-H,

the TEAE rates were similar between the lecanemab arm ( ) and placebo ( ).

Table 27: Treatment-emergent adverse events of special interest (Clarity AD, SAS)

Preferred term	Number of patients, n (%)	
	Lecanemab (n=898)	Placebo (n=897)
Patients with any TEAE of special interest		
ARIA-E	113 (12.6)	15 (1.7)
ARIA-H	155 (17.3)	81 (9.0)
Macrohaemorrhage	5 (0.6)	1 (0.1)
Superficial siderosis	50 (5.6)	21 (2.3)
Cerebral microhaemorrhage	126 (14.0)	68 (7.6)
Infusion-related reactions	237 (26.4)	66 (7.4)
Skin rash		
Other hypersensitivity		
Suicidal behaviour		
Suicidal ideation		

Source: Table 14.3.2.6.1, Clarity AD CSR[135]
Abbreviations: ARIA-E – amyloid-related imaging abnormality-oedema/effusion; ARIA-H – amyloid-related imaging abnormality-microhaemorrhage and haemosiderin deposit; n – number of patients in treatment group; SAS – Safety Analysis Set; TEAE – treatment-emergent adverse events.

B.2.10.4.1 ARIA-E

The overall incidence of ARIA-E (defined in Section B.2.3.1.2) was 12.6% for lecanemab, compared to 1.7% for placebo (Table 27). All ARIA-E events were considered treatment-related TEAEs, and the incidence of serious ARIA-E was in the lecanemab arm; there were in the placebo arm. Stratification by *APOE4* status and results are reported in the Clarity AD CSR, Table 13, Table 14.3.2.6.10.

Of the patients with ARIA-E, most treatment-emergent ARIA-E were radiographically mild (lecanemab: or moderate (lecanemab: in severity. There were categorised as having radiographically severe ARIA-E in the lecanemab arm and no patients in the placebo arm (Table 28). The rate of symptomatic ARIA-E was 2.8% in the lecanemab arm. Most treatment-emergent ARIA-E in the lecanemab arm were asymptomatic ( ), whilst all ARIA-E were asymptomatic in the placebo arm (Table 66, Appendix O1.8).

Table 28: Treatment-emergent ARIA-E by maximum radiographic severity (Clarity AD, SAS)

ARIA term Maximum radiographic severity	Number of patients, n (%)	
	Lecanemab (n=898)	Placebo (n=897)
Any ARIA-E	113 (12.6)	15 (1.7))
Mild	[redacted]	[redacted]
Moderate	[redacted]	[redacted]
Severe	[redacted]	[redacted]
Missing	[redacted]	[redacted]
Symptomatic ARIA-E	25 (2.8)	0 (0.0)
Asymptomatic ARIA-E	[redacted]	[redacted]

Source: Table 14.3.2.6.14, Clarity AD CSR[135]
Abbreviations: ARIA-E – amyloid-related imaging abnormality-oedema/effusion; n – number of patients in treatment group; SAS – Safety Analysis Set.

ARIA-E events in the placebo arm were randomly distributed over the course of treatment. For the first episode, most cases of treatment-emergent ARIA-E in the lecanemab arm occurred within the first 3 months of treatment ([redacted] (Table 67, Appendix O1.8).

Most patients in both treatment arms experienced ARIA-E without recurrence, with [redacted] lecanemab patients and [redacted] of placebo patients experiencing a second ARIA-E event. [redacted] lecanemab patients and [redacted] placebo patients experienced a third occurrence. [redacted] lecanemab patient experienced 4 episodes of ARIA-E.

Resolution is defined by resolution of both radiographic and clinical signs and symptoms of ARIA-E. The majority of ARIA-E resolved by four months since first onset in both treatment arms (lecanemab: [redacted] [redacted%]; placebo: [redacted] [redacted%]). All 113 cases of first ARIA-E events in the lecanemab group were resolved. In the placebo group, of the 15 cases of first ARIA-E, 12 resolved and 3 remained ongoing (Table 67, Appendix O1.8).

B.2.10.4.2 ARIA-H

ARIA-H is comprised of three subcategories; macrohaemorrhage, superficial siderosis, and cerebral microhaemorrhage. ARIA-H can occur in 2 settings: 1) isolated ARIA-H events not associated with ARIA-E and 2) concurrent with ARIA-E (i.e. having both ARIA-H and ARIA-E at the same time). This section presents overall, isolated and concurrent ARIA-H.

B.2.10.4.2.1 Overall ARIA-H

The overall incidence of ARIA-H was lower in the placebo arm (81/897 [9.0%]), compared to the lecanemab arm (155/898 [17.3%]) (CSR, Table 16, Table 19). The incidence of serious ARIA-H was [redacted]) in the lecanemab arm and [redacted]) in the placebo arm. A breakdown of overall treatment-

emergent ARIA-H by subcategory is available in CSR Table 19). Stratification by *APOE4* status and results are reported in the CSR, refer for more details.

Most treatment-emergent ARIA–H were radiographically mild (lecanemab: [redacted]; placebo [redacted] to moderate (lecanemab: [redacted]; placebo [redacted] in severity; with [redacted] on lecanemab and [redacted] on placebo reporting severe ARIA–H, mostly driven by cerebral microhaemorrhage events. In both treatment groups, most cases of ARIA-H was asymptomatic (lecanemab: [redacted]; placebo [redacted] and balanced across ARIA-H subcategories (CSR, Table 14.3.2.6.25).

Table 29: Treatment-emergent ARIA-H by maximum radiographic severity (Clarity AD, SAS)

Maximum radiographic severity	Number of patients, n (%)	
	Lecanemab (n=898)	Placebo (n=897)
Subjects with ARIA-H	155 (17.3)	81 (9.0)
Mild	[redacted]	[redacted]
Moderate	[redacted]	[redacted]
Severe	[redacted]	[redacted]
Missing	[redacted]	[redacted]

Source: Table 14.3.2.6.10.2, Clarity AD CSR[135]
Abbreviations: ARIA-H – amyloid-related imaging abnormality-microhaemorrhage and haemosiderin deposit; n – number of patients in treatment group; SAS – Safety Analysis Set.

Most cases of ARIA-H in both treatments arms were ongoing at the end of the Core Study. All cases of macrohaemorrhage with lecanemab or placebo were ongoing, which was expected (CSR, Table 14.3.2.6.38). Similar trends were observed in all ARIA-H subcategories.

Table 30: Time to onset of treatment-emergent ARIA-H (Clarity AD, SAS)

Time to onset of treatment-emergent ARIA-H	Number of patients	
	Lecanemab (n=898)	Placebo (n=897)
Total number of ARIA-H events	[redacted], n (%)*	[redacted], n (%)*
≤13 weeks visit	[redacted]	[redacted]
>13 to ≤27 weeks visit	[redacted]	[redacted]
>27 to ≤39 weeks visit	[redacted]	[redacted]
>39 to ≤53 weeks visit	[redacted]	[redacted]
>53 to ≤65 weeks visit	[redacted]	[redacted]
>65 weeks visit	[redacted]	[redacted]

Source: Table 14.3.2.6.28, Clarity AD CSR[135]

* Percentage based on patients with ARIA-H.
Based on scheduled visit for safety MRI and a visit window of ±8 days is allowed for each visit.
Abbreviations: ARIA-H – amyloid-related imaging abnormality-microhaemorrhage and haemosiderin deposit; n – number of patients in treatment group; SAS – Safety Analysis Set.

B.2.10.4.2.2 Isolated ARIA-H

Isolated ARIA-H events were similar between lecabemab (80/898 [8.9%]) and placebo (70/897 [7.8%]) overall and by maximum radiographic severity (Table 31). Isolated ARIA-H events occur throughout the course of treatment in both treatment arms (CSR, Figure 14.3.2.6.2.2). Rates of symptomatic isolated ARIA-H were similar between lecanemab (6/898 [0.7%]) and placebo (2/897 [0.2%]) (CSR, Table 14.3.2.6.10.5).

Table 31: Treatment-emergent isolated ARIA-H by maximum radiographic severity (Clarity AD, SAS)

Maximum radiographic severity	Number of patients, n (%)	
	Lecanemab (n=898)	Placebo (n=897)
Subjects with ARIA-H	80 (8.9)	70 (7.8)
Mild	[redacted]	[redacted]
Moderate	[redacted]	[redacted]
Severe	[redacted]	[redacted]
Missing	[redacted]	[redacted]

Source: Table 14.3.2.6.10.6, Clarity AD CSR[135]
Abbreviations: ARIA-H – amyloid-related imaging abnormality-microhaemorrhage and haemosiderin deposit; n – number of patients in treatment group; SAS – Safety Analysis Set.

B.2.10.4.2.3 Concurrent ARIA-E and ARIA-H

The overall incidence of concurrent ARIA-E and ARIA-H was lower in the placebo arm (9/897 [1.0%]) compared to the lecanemab arm (74/898 [8.2%]) (Table 32). The onset time, distributions, and symptoms of concurrent ARIA-E and ARIA-H follow the pattern of ARIA-E (CSR, Table 14.3.2.6.10.7, Table 14.3.2.6.25.2, Table 14.3.2.6.28.2, Figure 14.3.2.6.2.3). The excess incidence of ARIA-H in the lecanemab arm is most likely due to ARIA-H that occurs during the onset or resolution of ARIA-E.

Table 32: Treatment-emergent concurrent ARIA-H by maximum radiographic severity (Clarity AD, SAS)

Maximum radiographic severity	Number of patients, n (%)	
	Lecanemab (n=898)	Placebo (n=897)
Subjects with ARIA-H	74 (8.2)	9 (1.0)
Mild	[redacted]	[redacted]
Moderate	[redacted]	[redacted]
Severe	[redacted]	[redacted]
Missing	[redacted]	[redacted]

Source: Table 14.3.2.6.10.7, Clarity AD CSR[135]
Abbreviations: ARIA-H – amyloid-related imaging abnormality-microhaemorrhage and haemosiderin deposit; n – number of patients in treatment group; SAS – Safety Analysis Set.

B.2.10.4.3 Infusion-related reactions

Infusion-related reactions, which include the preferred terms 'infusion related reaction' and 'infusion site reaction', were reported for 237 (26.4%) lecanemab patients compared to 66 (7.4%) placebo patients (Table 33). Of these, the majority occurred with the first infusion ([redacted] for placebo and 178 [75.1%] for lecanemab) and most patients had only 1 infusion-related reaction ([redacted]

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

Most patients who experienced an infusion-related reaction continued to the next visit (lecanemab:[redacted] placebo [redacted] [redacted]of which [redacted] lecanemab patients and [redacted] placebo patients received at least one preventative medication (nonsteroidal anti-inflammatory drugs [NSAIDs], antihistamines and glucocorticoids) prior to subsequent infusions. Of these, [redacted] lecanemab patients and [redacted] [redacted]) placebo patients did not have subsequent infusion-related reactions.

Out of the [redacted] lecanemab and [redacted] placebo patients who experienced an infusion-related reaction but did not receive a preventative medication prior to subsequent infusions, [redacted] and [redacted] patients did not have a subsequent infusion-related reaction, respectively.

Table 33: Summary of infusion-related reactions by maximum grade (Clarity AD, SAS)

NCI-CTCAE Grade	Number of patients, n (%)	
	Lecanemab (n=898)	Placebo (n=897)
Any grade	237 (26.4)	66 (7.4)
Grade 1	[redacted]	[redacted]
Grade 2	[redacted]	[redacted]
Grade 3	[redacted]	[redacted]
Grade 4	[redacted]	[redacted]
Grade 5	[redacted]	[redacted]
Missing	[redacted]	[redacted]

Source: Table 12 Summary of Infusion-Related Reactions by Maximum Grade and Use of Preventative Medications – Core Study (Safety Analysis Set), Clarity AD CSR[135]
Abbreviations: SAS – Safety Analysis Set; CTCAE = Common Terminology Criteria for Adverse Events

B.2.10.5 Deaths

During the Clarity AD core study, a similar proportion of deaths occurred in the lecanemab (6/898 [0.7%]) and placebo (7/897 [0.8%]) arms (Table 34). No deaths were related to lecanemab and no deaths due to treatment-emergent ARIA. There were 13 treatment-emergent deaths, and 2 deaths were nontreatment-emergent (i.e. occurred >30 days after the last study treatment administration). One nontreatment-emergent death occurred in the lecanemab arm 36 days after the last dose of lecanemab. The death was due to diabetic ketoacidosis and was not considered to be related to lecanemab treatment. One nontreatment-emergent death due to cardio-respiratory arrest occurred in the placebo arm 49 days after the last dose.

Additionally, a similar proportion of deaths occurred in the lecanemab ([redacted] and placebo (i.e. newly treated core study placebo subjects) [redacted] groups in the Clarity AD OLE study. Both of the deaths in the lecanemab group occurred in patients with significant comorbidities and risk factors including anticoagulation, which are thought to have contributed to macrohaemorrhage or death. Full details of deaths in the OLE can be found in Appendix F.

A summary of TEAEs leading to death in the core study is provided in Table 34.

Table 34: Summary of treatment-emergent deaths (Clarity AD, SAS)

MedDRA system organ class preferred term	Number of patients, n (%)	
	Lecanemab (n=898)	Placebo (n=897)

Subjects with any TEAE leading to death	6 (0.7)	7 (0.8)
Cardiac disorders	[redacted]	[redacted]
Myocardial infarction	[redacted]	[redacted]
General disorders and administration site conditions	[redacted]	[redacted]
Death	[redacted]	[redacted]
Infections and infestations	[redacted]	[redacted]
COVID-19	[redacted]	[redacted]
Neoplasms benign, malignant, and unspecified (including cysts and polyps)	[redacted]	[redacted]
Metastases to bone	[redacted]	[redacted]
Metastases to meninges	[redacted]	[redacted]
Pancreatic carcinoma	[redacted]	[redacted]
Nervous system disorders	[redacted]	[redacted]
Cerebrovascular accident	[redacted]	[redacted]
Haemorrhage intracranial	[redacted]	[redacted]
Respiratory, thoracic, and mediastinal disorders	[redacted]	[redacted]
Acute respiratory failure	[redacted]	[redacted]
Respiratory failure	[redacted]	[redacted]

Source: Table 14.3.2.1.1 Clarity AD CSR[135]
Non-treatment-emergent deaths not included.
Abbreviations: MedDRA – Medical Dictionary for Regulatory Activities; n – number of patients in treatment group; SAS – Safety Analysis Set.

B.2.10.6 Safety conclusions

The safety data from Clarity AD demonstrate that lecanemab is tolerable and safe in the treatment of patients with early AD, with a safety profile consistent with other dose regimens evaluated in Study 201.[135,157]

The overall incidence of TEAEs (lecanemab: 88.9%; placebo: 81.9%) and TESAEs was very similar between the two arms. The most common AEs occurring in the lecanemab arm were infusion-related reactions (26.3%) and ARIA-E (12.6%). Of patients who had infusion-related reactions in the lecanemab arm, [redacted]% continued to the next dose and approximately two thirds of these patients had no further infusion site reactions, with or without preventative treatment.

Potential risks associated with ARIA are monitorable and manageable in clinical practice. In the core Clarity AD study, ARIA-E occurred early in treatment, was mostly asymptomatic and resolved spontaneously, regardless of radiographic severity. Of patients who had ARIA-E, [redacted]% were deemed serious, and [redacted]% of patients discontinued treatment due to ARIA-E. The median time to resolution from onset for first ARIA-E was just 90 days in the lecanemab arm. The time of onset

was also early in the lecanemab arm, with 70.8% of ARIA-E events occurring in the first 13 weeks of study treatment. Most patients in both treatment groups experienced ARIA-E without recurrence, with just 3.1% of lecanemab patients experiencing a second event. The risks of ARIA-E in clinical practice appear to be manageable through routine MRI monitoring and dose management of lecanemab.

Overall, very low numbers of patients discontinued treatment due to TEAEs (placebo vs lecanemab 62 [6.9%] vs 26 [2.9%] Table 25). This indicates that patients are likely to stay on lecanemab treatment and therefore continue to benefit from the strong efficacy profile demonstrated in Clarity AD.

Deaths occurred in 0.7% of patients in the lecanemab arm and 0.8% in the placebo group, none of which were related to lecanemab or occurred with ARIA, as determined by the investigator.

Overall, lecanemab has an acceptable safety profile similar to the safety and tolerability observed in previous studies of other anti-amyloid therapies.[135,157] Patients are likely to stay on treatment and continue to receive the cognitive benefits of lecanemab treatment with only a small risk of symptomatic ARIA events that can be mitigated by regular MRI and dose suspension.

B.2.11 Ongoing studies

The OLE of Clarity AD is an ongoing single-arm Phase III extension study including patients who participated in the core Clarity AD study (B.2.3.1). All patients in the OLE receive open-label lecanemab 10 mg/kg biweekly for at least six months and up to a maximum of 48 months in the clinic, until the drug is commercially available in the country where the patient resides, or until the benefit-to-risk assessment from treatment with lecanemab is no longer considered favourable, whichever comes first. Any patient who completed 18 months treatment in the core study (Visit 42 [Week 79]) had the option to continue into the OLE if inclusion and exclusion criteria were met. For the patients who continued into the OLE period, patients randomised to lecanemab continued treatment whilst patients randomised to placebo switched to lecanemab. Further details on patient flow in the OLE are available in Section B.2.3.1. Full details of the OLE are presented in Table 35.

Table 35: Open-label extension of Clarity AD

Trial design	Global, open-label, multicentre, longitudinal, single-arm, Phase III extension study in patients with early AD who were previously in the core Clarity AD study and completed Week 79
Eligibility criteria	• Completion of the core study • Continued willingness from the study partner to provide follow-up information throughout the OLE • Provision of the patients informed consent for the OLE • Willingness and ability to comply with all aspects of the OLE protocol
Settings and locations where the data were collected	247 study locations in US, Australia, Canada, China, France, Germany, Italy, Japan, Republic of Korea, Russia, Singapore, Spain, Sweden, UK Six sites in the UK
Trial drugs – interventions and comparators	• Lecanemab 10 mg/kg IV biweekly • Optional subcutaneous substudy (US and Japan only) – lecanemab 720 mg subcutaneous weekly
Primary endpoints	Primary outcomes • Number of participants reporting one or more TEAEs • Change from core study baseline in CDR-SB
Exploratory endpoints	Exploratory endpoints • Change from core study baseline in the following: o ADAS-Cog14, ADCOMS, ADCS MCI-ADL, and modified iADRS o Brain amyloid and Tau PET levels (amyloid PET: amyloid PET using Centiloids and amyloid PET SUVR composite; Tau PET: tau PET SUVR in whole cortical grey matter region of interest (ROI), meta-temporal ROI, frontal ROI, cingulate ROI, parietal ROI, occipital ROI, medial temporal ROI, and temporal ROI and Tau^{IQ} global Tau load [algorithm for the quantification of Tau PET scans]) o Blood and CSF biomarkers (neurogranin [CSF only], NFL, Aβ[1-42], Aβ[1-40], plasma Aβ42/40 ratio, t-Tau, and p-Tau [including, but not limited to p-Tau181]) o vMRI biomarkers

	○ EQ-5D-5L, QOL-AD, and ZBI • Proportion of patients who converted from amyloid PET positive at core study baseline to amyloid PET negative at post-baseline by visual read, SUVR, and Centiloids • Correlation between clinical changes (CDR-SB, ADAS-Cog14, ADCOMS, ADCS MCI-ADL, and modified iADRS) and changes in biomarkers of AD pathology (including but not limited to, amyloid PET, Tau PET, blood, and CSF biomarkers [Aβ[1-42], Aβ[1-40], plasma Aβ42/40 ratio, neurogranin, NFL, t-Tau, and p-Tau]) • Assessment of the characteristics, comorbidities, treatments, associated costs for patients with early AD, and study partner burden at baseline, before study enrolment, during study participation (including core study and OLE), and after study completion
Statistical analyses	A MMRM will be used to analyse changes from core study baseline in the following: • Clinical endpoints: CDR-SB, ADAS-Cog14, ADCOMS, ADCS MCI-ADL and modified iADRS • EQ-5D-5L, QOL-AD, and ZBI • Biomarkers: amyloid PET using Centiloids, amyloid PET SUVR composite, Tau PET SUVR, in whole cortical grey matter ROI, meta-temporal ROI, frontal ROI, cingulate ROI, parietal ROI, occipital ROI, medial temporal ROI, and temporal ROI and Tau^{IQ} global Tau load, blood and CSF biomarkers (Aβ[1-42], and Aβ[1-40], plasma Aβ42/40 ratio, neurogranin [CSF only], NFL, t-Tau and p-Tau [including, but not limited to p-Tau181]), and vMRI

Abbreviations: AD – Alzheimer's disease; ADAS-Cog14 – Alzheimer's Disease Assessment Scale-Cognitive subscale; ADCOMS – Alzheimer's disease composite score; ADCS MCI-ADL – Alzheimer's Disease Cooperative Study – Activities of Daily Living for Mild Cognitive Impairment; CDR-SB – Clinical Dementia Rating – Sum of Boxes; CSF – cerebrospinal fluid; iARDS – Integrated Alzheimer's disease rating scale; MMRM – mixed model for repeated measures; NFL – neurofilament light chain; OLE – open-label extension; PET – positron emission tomography; QOL-AD – Quality of life in Alzheimer's disease; ROI – region of interest; SUVR – standard uptake value ratio; vMRI – volumetric magnetic resonance imaging; ZBI – Zarit's Burden Interview.

B.2.12 Interpretation of clinical effectiveness and safety evidence

B.2.12.1 Principal findings of the evidence base

Clarity AD shows that lecanemab 10 mg/kg biweekly provides meaningful benefits for patients with early AD and their caregivers through the convergence of evidence across multiple measures of cognition, function, disease progression, HRQoL, caregiver burden, and biomarkers. The significant responses shown across all independent clinical, biomarker, and QoL scales that encompass disease progression in early AD provide more insight into therapeutic response than could be achieved through single-measure approaches.

Lecanemab treatment showed persistent delay in the neuropathological process, underpinned by removal of amyloid and impact on downstream biomarkers, including slowing of Tau accumulation by tau PET and improvement of inflammatory, synaptic, and neurodegeneration biomarkers. These data provide convincing evidence of the disease modifying effect of lecanemab, indicating that lecanemab has the capacity to address the unmet needs of patients, caregivers, and the healthcare system by slowing the clinical decline of AD.

Whilst there is no consensus on MCIDs for outcomes in AD trials, meaningful within-patient change thresholds have been established to indicate meaningful progression among patients. A 20-30% reduction in decline compared to placebo in CDR-SB is frequently cited as an appropriate benchmark for clinical meaningfulness.[159,160,183,186] MCIDs are most applicable to symptomatic therapies for which the difference between treatment and placebo remains stable after the initial therapeutic response. With DMTs such as lecanemab, an increasing treatment–placebo difference is observed over the course of the trial, suggesting that further separation would be seen over a longer time duration, beyond the considerable benefit observed within the trial timeframe.[187]

The results of Clarity AD demonstrate that lecanemab significantly reduced cognitive and functional decline in early AD patients, as measured by a significant reduction in the deterioration of mean CDR-SB from baseline compared to placebo at 18 months (-27.1%, Section B.2.6.1). This effect was seen across all six domains of the CDR-SB (ranging from -21.2% to -29.9%) and was maintained across subgroup analyses, including both MCI and mild AD subgroups. These results are relevant since CDR-SB, the primary endpoint in Clarity AD, was recommended as a suitable tool for clinical investigation of novel medicines for AD by the EMA.[188] Assessment of time to worsening of global CDR score showed that lecanemab reduced the risk of progression to the next stage of AD by 31% (see Section B.2.6.4). Additionally, slope analysis suggested that continued improvement would be seen with longer treatment, with increasing separation over time translating to a 5.3 month delay in disease-related progression at 18 months increasing to a 7.5 month delay at 25.5

months, based on CDR-SB. As a result, patients spend longer in the more independent stages of the AD, and therefore maintain independence and functionality for longer, improving both patient and carer QoL (Section B.2.6.5).[189]

Lecanemab also significantly reduced decline in cognitive status compared to placebo in ADAS-Cog14 (25.8%, Section B.2.6.2.3) and ADCOMS (23.5%, Section B.2.6.2.4). The reduction in decline seen with these measures and the associated reduction in risk of progression to the next stage of AD demonstrate that lecanemab enables individuals to spend more time in less severe stages of disease, which is of great importance to patients and caregivers. One caregiver described how within a year of diagnosis their mother 'didn't know what day, month, week, year it was' and that they had lost the 'ability to read, write and draw', emphasising the value of extending time in less severe stages of disease.[190] Delay in progression from early AD to moderate AD translates to patients only requiring prompting with personal care, rather than frequent assistance.[191] Patients may be able to maintain hobbies and intellectual interests for longer, rather than abandoning these due to cognitive and functional impairment. With a delay in progression, patients are able to remain engaged in social groups for longer, before progressing to later stages of disease in which they may be unable to function independently and may struggle to communicate with others.[191,192] Impacts like these show the importance of delaying progression to the next stage of AD.

Patients receiving lecanemab also showed less decline in functional autonomy, as measured by ADCS MCI-ADL (36.6% less decline), with consistent results seen across all items (see Section B.2.6.2.5). A single point change in ADCS MCI-ADL can mean a shift from performing an activity unsupervised to requiring supervision, or a shift from requiring supervision to requiring physical assistance by a care partner; results from Clarity AD showed a 2.016-point difference between lecanemab and placebo. Therefore, lecanemab could bring tangible benefits to patients and carers by the slowing of progression on this scale. A recent meta-analysis of outcomes in AD that are meaningful to patients, carers, and health care professionals identified maintenance of ADL function as meaningful to all three stakeholder groups in over eight independent studies.[193]

On these four clinical measures lecanemab showed a consistent, statistically significant reduction in cognitive and functional decline compared to placebo at 18 months, ranging from 23.5% (ADCOMS) to 36.6% (ADCS MCI-ADL). The consistent delay in progression by slope analysis on CDR-SB (5.3 months preserved over the 18-month study), ADAS-Cog14 ([redacted] months preserved over the 18-month study), and ADCS MCI-ADL ([redacted] months preserved over the 18-month study) and by time-to-event analysis of progression to next stage of AD (HR = 0.69) together support meaningful benefits in independent outcomes affected in early AD. Each clinical measure provides vital information and together these comprehensively capture different clinically meaningful domains of cognitive and functional ability

affected in patients with AD. As such, these results demonstrate the broad efficacy of lecanemab across varied aspects of AD.

The benefits in cognitive and functional outcomes with lecanemab treatment seen in Clarity AD are supported by biomarker outcomes, providing a biological basis for the treatment effects. Brain amyloid is a defining pathological feature of AD that precedes and predisposes to tauopathy, neurodegeneration, and cognitive decline (Section B.1.3.1.1). As such, brain amyloid is one of the most important targets for halting AD pathology and slowing the progression of AD. Changes in amyloid biomarkers therefore reflect an impact on the underlying pathophysiological disease processes of AD, indicating a disease modifying effect. Lecanemab showed a statistically significant reduction in amyloid plaque burden vs. placebo at all timepoints and a statistically significant difference vs. placebo in the proportion of patients converting to amyloid negativity at 18 months (60.4% vs 0.6%, Section B.2.6.2.2). Patient-level analysis demonstrated a correlation between brain amyloid and CDR-SB, providing reliable evidence of biomarker change as a surrogate endpoint for clinical efficacy (see Section B.2.6.3). Moreover, consistent benefit was observed with lecanemab treatment in downstream markers of the amyloid cascade, including slowing of tau PET accumulation, reduction in validated markers of astrocyte activation (plasma GFAP), synapse dysfunction (CSF neurogranin), and neurodegeneration (CSF t-tau). These results suggest that the slowing of cognitive decline seen through treatment with lecanemab is a result of modification of the course of disease, rather than symptomatic improvements alone.

Lecanemab was associated with a greater relative preservation of HRQoL and reduction in caregiver burden compared to placebo, as reported by patients and their study partners, with consistent benefits seen across different scales, within items, and within the vast majority subdomains of these scales. The consistency of these results provides strong additional evidence for patient-relevant benefits to both lecanemab patients and their caregivers, beyond the clinical benefits demonstrated through changes in biomarkers and cognitive and functional measures.

Lecanemab has a well characterised safety profile, with safety analysis from Clarity AD demonstrating that lecanemab is tolerable in the treatment of patients with early AD. Patients that experienced AEs remained on treatment or resumed treatment after temporary suspension, ensuring that the benefits of lecanemab were not withheld. ARIA-E was the most frequently observed AE amongst lecanemab-treated patients, but was generally observed in the first three months, was mostly mild-to-moderate radiographically in severity and mostly asymptomatic, did not lead to discontinuation if mild or moderate, and resolved within four months. Moreover, the risk of ARIA-E in clinical practice can be mitigated with routine MRI monitoring and dosing management, as per the Clarity AD protocol. For these reasons, the benefits of lecanemab outweigh the potential risks.

The Clarity AD trial represents an unprecedented and foundational advance in the search for a disease-modifying treatment for AD. It is the first to show an unequivocal effect in changing the rate of decline on diverse clinical, cognitive, and functional endpoints, converging with validated, AD-associated brain, cerebrospinal fluid, and blood biomarker endpoints.[194] Patients treated with lecanemab in Clarity AD remain in earlier stages of disease for longer, where they are able to function relatively independently, the importance of which is consistently highlighted by patients, care partners, and clinicians.[193,195]

B.2.12.2 Strengths and limitations of the evidence base

B.2.12.2.1 Strengths of the evidence base

Clarity AD provides robust evidence of the clinical benefit of lecanemab in early AD, demonstrating a reduced rate of clinical decline and a reduction in brain amyloid. Patient-level analysis showed a correlation between brain amyloid and CDR-SB, providing reliable evidence of biomarker change as a surrogate endpoint for clinical efficacy. Mediation analyses indicated that 80% of the effect of lecanemab on CDR-SB can be explained by reduction in amyloid PET (Centiloids).[138] This indicates that reducing the levels of Aβ protofibrils provides an effective treatment approach to early AD that results in the arrest of progressive neuronal toxicity and other pathological processes associated with AD.

Lecanemab demonstrated a statistically significant effect on established, validated, and globally accepted endpoints, covering a range of cognitive and functional aspects. These endpoints represent clinically meaningful scales that directly measure how a patient thinks, feels, or functions, with every domain within the instruments being considered to measure a clinically meaningful concept for AD patients.[195]

The 10 mg/kg biweekly dosing strategy adopted in Clarity AD was chosen following the Phase II dose-finding Study 201, which established this dose as the most effective dosing regimen for lecanemab.[53] Five dosing schedules were explored in Study 201, with lecanemab 10 mg/kg monthly and 10 mg/kg biweekly being identified as potential effective dose 90% (ED90) doses early in the study, and the 10 mg/kg biweekly dose determined to be the final ED90 dose, defined as the simplest treatment group that achieved at least 90% of the modelled maximum treatment effect, based on ADCOMS. The use of a robust dose-finding study provided confidence in the dosing strategy adopted for Clarity AD.

Use of amyloid biomarker confirmation for patient eligibility ensured that only patients with the target pathophysiology were treated. Targeting patients during early AD rather than moderate AD increased the chance to meaningfully slow decline. Targeting soluble aggregated protofibrils of amyloid was also advantageous since these are believed to be the toxic species of amyloid (see Section B.1.2), while also robustly removing amyloid plaque species.

Clarity AD had a diverse patient population due to its broad eligibility criteria, worldwide site selection (14 countries in North America, Europe, Asia, Australia), inclusion of patients with multiple comorbidities, community outreach, and decentralised activities. It is essential that clinical trials include diverse patient populations so that all communities can benefit from scientific research and advances.[196] This is particularly relevant in AD, since there is a greater risk of dementia in South Asian and Black people when compared to white people and in women, with two in three of those with dementia in the UK being female.[197-198] Representation of these groups in Clarity AD was reflective of the UK general population (see below), thus ensuring that generalisability to the wider population is not compromised.[137]

The results of the Clarity AD trial are relevant to the decision problem specified in the NICE final scope proposing the use of lecanemab for people early AD. The external validity and generalisability of Clarity AD to UK clinical practice is supported by:

- **Population:** Patients in Clarity AD had early AD as confirmed by positive amyloid PET or CSF biomarkers for brain amyloid pathology reflecting the license wording for lecanemab. Clinical experts confirmed in a clinical advisory board held in May 2023 that the baseline characteristics of Clarity AD were reflective of the population expected to receive lecanemab in UK clinical practice.[137]
- **Intervention:** Lecanemab 10 mg/kg biweekly IV was evaluated in line with its licensed indication.
- **Comparators:** Patients in either arm of Clarity AD could enter the study whether they were receiving an approved AD treatment such as AChEIs or memantine, or not receiving AD-specific treatments. This is in line with the license wording for lecanemab supporting its use as an add-on treatment to the patient's current care. In both arms of Clarity AD, approximately half of patients were already receiving AD medication. In Europe, approximately 31% of MCI patients receive AChEIs and 8% receive memantine (both off-label since no treatments are recommended for MCI), and up to 89% of mild AD patients receive AChEIs and 7-21% receive memantine.[199]
- **Outcomes:** Key outcomes relevant for decision making were assessed in the Clarity AD trial and used in the economic analysis described in Section B.3 (cognitive and functional impairment, mortality, patient HRQoL, carer HRQoL, adverse effects of treatment).

B.2.12.2.2 Limitations of the evidence base

AD is a chronic condition, therefore extrapolation of this efficacy data must be used to estimate treatment effect beyond the 18 month duration of the Clarity AD core study (Section B.3.3.1.2). Extrapolation is widely used in health technology assessments, including NICE appraisals.[200] It is expected that the ongoing OLE

study will provide further insights on the progression of AD and effect of lecanemab beyond 18 months.

Clarity AD was conducted during the COVID-19 pandemic, leading to challenges such as missed doses, delayed assessments, and intercurrent illnesses. Despite this, the dropout rate was less than 17.2%, and a sensitivity analysis evaluating the impact of missed doses was consistent with the primary endpoint analysis, indicating that these dropouts were random and did not affect the study results. Additionally, aspects of the Clarity AD protocol were adapted in response to the COVID-19 pandemic to overcome these challenges, as mentioned in Section B.2.3.1 and described in detail in Appendix M.

One potential limitation stems from the use of post baseline data without imputation of missing values. However, a sensitivity analysis using a standard ITT population with imputation produced comparable results to the primary endpoint analysis. Instances of ARIA might have led both participants and researchers to make assumptions about the trial-group allocations to treatment. To mitigate this potential bias, the investigators ensured that clinical raters remained uninformed about the safety evaluations and trial-group assignments. Furthermore, sensitivity analyses to investigate the influence of ARIA on clinical outcomes revealed that ARIA did not exert any impact on the outcomes. The sensitivity analysis involved repeating the primary MMRM analysis whilst censoring data after an ARIA event. Results were consistent with the primary analysis.

B.2.12.3 Conclusion

Clarity AD demonstrates that treatment with lecanemab leads to statistically significant and clinically meaningful reductions in decline in clinical measures of cognition and function compared to placebo at 18 months. This is linked to reduction in biomarkers associated with the underlying pathology of AD. The strong efficacy findings for lecanemab in Clarity AD coupled with the well characterised safety profile and statistically significant differences in patient and carer HRQoL unequivocally demonstrate the benefits of treating early AD patients with lecanemab.

AD is an insidious disease for which there are limited to no short-term symptomatic treatments available in the UK, dependent on stage of disease. There are currently no approved pharmacological treatments nor published treatment guidelines for patients with MCI due to AD. Limited treatments exist for patients with mild AD, however these therapies provide modest, temporary benefit to symptoms which is rapidly lost after treatment discontinuation, and do not slow amyloid accumulation nor slow the spread of NFTs, the drivers of disease progression. This leaves patients feeling anxious and waiting in limbo for their disease to progress to the next stage before being able to be treated.

Patient and care partner output from Clarity AD show that the benefits offered by lecanemab are clinically meaningful.[195] All therapies have associated risks, and for

monoclonal antibodies directed against amyloid, the risk of greatest concern is ARIA. Extensive analysis in Clarity AD showed that the risk of ARIA was monitorable and manageable.

Considering the extreme unmet need in AD, owing to the low quality of life of patients and the lack of a DMT at any stage of disease, lecanemab would provide hope for early AD patients who face a journey through progressive disease.

Lecanemab is the first treatment that targets the underlying pathophysiology of AD to receive regulatory approval for early AD in US and Japan.[201,202] Similar to the value of the first treatments for HIV or multiple sclerosis, the value of lecanemab could extend beyond the immediate benefits to patients, and herald investment in AD and development of new therapeutic agents and targets.

B.3 Cost-effectiveness

Summary of cost-effectiveness analysis

- A *de novo* Markov model was developed to evaluate the cost-effectiveness of lecanemab versus standard of care (SoC) in adult patients with early AD and confirmed Aβ pathology.
- The model consisted of nine health states across community and institution: MCI due to AD, Mild AD, Moderate AD, Severe AD, and death, defined by CDR-SB.
- AD progression up to 18 months for lecanemab and SoC was based on the ITT population of Clarity AD. SoC risk was extrapolated using natural history data from Potashman et al.[203] The relative effect of lecanemab was modelled via hazard ratios for time to worsening of CDR-SB.
- The rate of institutionalisation was taken from a UK patient registry analysis reported by Knapp et al.[204] Mortality was informed by Crowell et al., who report HRs derived from the NACC database.[205]
- MCI and mild AD community health state utilities were informed by patient reported EQ-5D data from Clarity AD. Farina et al. was used to inform patient-by-proxy utilities for moderate and severe AD community health states, as well as patient-reported and patient-by-proxy insititutionalisation HRQoL effects for MCI and mild AD and for moderate and severe AD, respectively.
- Costs associated with drug acquisition and administration, management of AEs, disease monitoring, direct medical and non-medical costs (including the cost of institutionalisation) were included for all modelled treatments. Additionally, the costs of diagnostic testing were included for lecanemab only. All unit costs were sourced from the relevant national UK sources. Healthcare resource use and other aggregate costs were sourced from previous NICE TAs where relevant, or external literature, with any missing data provided by clinical opinion.

Summary of cost-effectiveness results

- The base-case analysis estimates that lecanemab generates additional QALYs ([redacted]) at higher average costs [redacted]) when compared to SoC, driven by delayed time to moderate and severe AD.
- The PSA results were consistent with the deterministic base-case results. In the OWSA, the parameters with the greatest impact on the base-case ICER were the time to worsening HRs for lecanemab versus SoC.
- The validity of the deterministic results was further supported by extensive scenario analyses, which indicate that the base case analysis is conservative.
- All key model inputs and modelling assumptions have been validated by UK clinicians, with internal, external, and cross-validation steps taking place.

The analysis estimates that lecanemab generates meaning benefits for patients and caregivers versus SoC. Given the acute need for a DMT in early AD, there is a clear place for lecanemab in the NHS pathway. Lecanemab is also expected to generate benefits that are not captured in the QALY framework, meaning the true value of lecanemab to society may be underestimated in this analysis.

B.3.1 Published cost-effectiveness studies

A SLR was conducted to identify cost-effectiveness studies relevant to the decision problem. The SLR was conducted iteratively, with the original SLR conducted in 2016 and four SLR updates conducted up until August 2023. A summary of the timeframes covered by each of the reviews is presented in Table 36. Full details of the SLR strategy, study selection process, and results are presented in Appendix G.

Table 36: Summary of the cost-effectiveness SLRs conducted to date

Year of search	2023 (current)	2021	2020	2018	2016
Search dates	27th June 2021 to 31st August 2023	20th February 2020 to 27th June 2021	28th October 2018 to 20th February 2020	1st January 2016 to 27th November 2018*	Database inception to 29th March 2016

*Additional reviews conducted by (Hernandez 2016) and (ROADMAP 2017) were used as supplementary sources.
Abbreviations: SLR – Systematic literature review

Across all reviews, 20 UK-specific studies were identified although none evaluated the cost-effectiveness of lecanemab (Appendix G1.2.1, Table 38). Of these, 11 used a Markov modelling approach.[206–216] Seven studies used a discrete-event simulation (DES) structure[217–223] while the remaining two studies did not provide enough detail to determine the modelling approach used.[224,225] Green et al. 2005[209] and Loveman et al. 2006[210] use the same approach as used in TA111 (the original appraisal of donepezil, galantamine, rivastigmine and memantine for AD), a Markov modelling approach, and Peters et al. 2013[207] and Hyde et al. 2013[207] refer to the same approach which is also used in TA217 (review of TA111), which was a Markov time-to-institutionalisation model developed by the Assessment Group based on TA111.

Nine studies utilised health states defined by AD severity,[211,212,214,216,218,220–222,224] while nine did not consider disease severity and instead utilised health states based on whether patients remained in the community or had entered institutionalisation (referred to as full time care in some models). The remaining two studies did not sufficiently detail the health states evaluated. Of the studies which utilised health states based on AD severity, one study used CDR-SB,[220] seven used MMSE,[211,212,214,216,218,222,224] and one used a combination of MMSE, NPI, ADL, and IADL.[221] The studies using MMSE were typically older, with the majority being published before 2010.

The time horizons adopted in the analyses ranged from 16-months to lifetime, and 16 of the 20 studies considered pharmacological interventions, two were non-pharmacological interventions and two were hypothetical DMTs for AD. Twelve

studies adopted an NHS and PSS perspective,[206–210,212,216–219,223,224] while six studies considered a societal perspective.[213,215,220–222,225] Two studies did not state the perspective used.[211,214]

B.3.2 Economic analysis

No published economic evaluations of lecanemab were identified that matched the decision problem, therefore a *de novo* cost-effectiveness model (CEM) was developed to evaluate the clinical and cost-effectiveness of lecanemab in alignment with the final scope (Table 1).

B.3.2.1 Patient population

The population evaluated is adult patients with MCI due to AD or mild dementia due to AD (early AD) and confirmed Aβ pathology in alignment with the anticipated positioning of lecanemab and the final scope (Section B.1.1).[226] The baseline population characteristics used in the analysis (Table 37) are reflective of the Clarity AD ITT population and were considered generalisable to UK clinical practice.[137]

To reflect the final scope, scenario analyses are presented based on the MCI due to AD and mild AD clinical subgroups (Section B.3.11.3).

Table 37: Baseline patient characteristics in the model

Patient characteristics	Value (SE)	Source
Age (years, mean)	71.2 (7.84)	Clarity AD, Table 14.1.4.1.1 [135]
Female (proportion)	52.3% (0.01)	
Weight, kg (mean [SD])	69.8 (12.54)	
Baseline health state MCI due to AD	78.8% (0.01)	Clarity AD, Table 14.2.3.8.1 [135]
Baseline health state mild dementia due to AD	21.2% (0.01)	

Abbreviations: AD – Alzheimer's disease; kg – Kilogram; MCI – Mild cognitive impairment; SE – standard error

B.3.2.2 Perspective

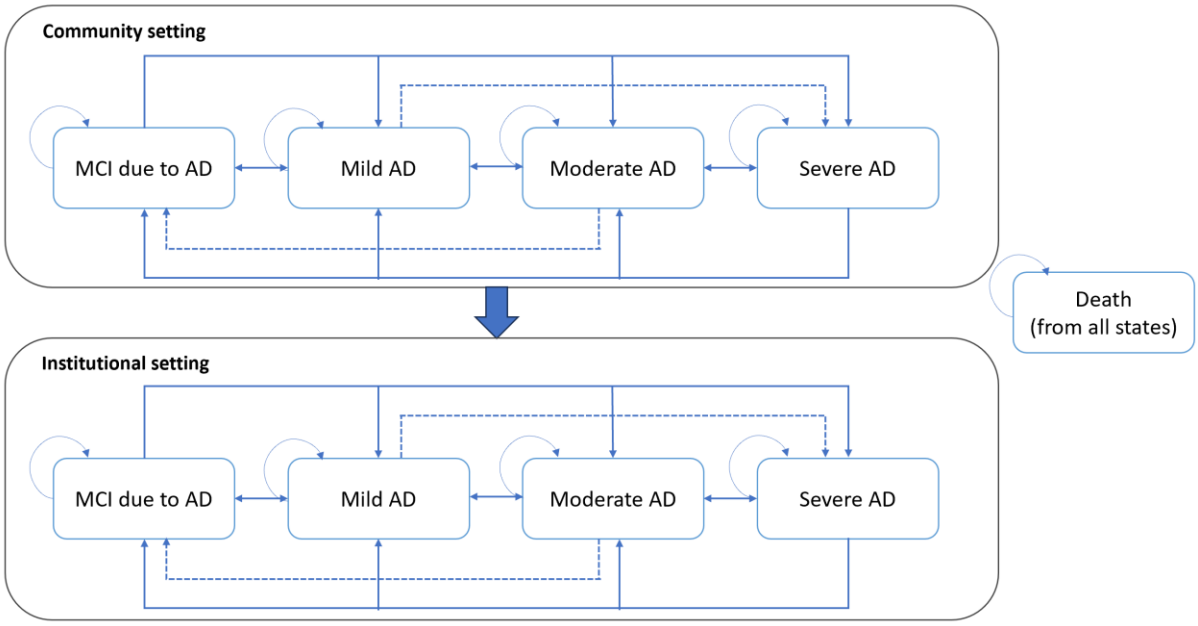
The base case analysis adopts an NHS and PSS perspective in England and Wales, hence all health effects for patients and caregivers are considered in line with the NICE reference case.

As described in Section B.1.3.5.2, unpaid care accounts for 40% of the total costs of dementia care in the UK (£13.9 billion in 2019).[104] As outlined in Section 4.4.24 of NICE's methods manual for health technology evaluations, when care by family members, friends, or a partner (i.e., unpaid care) might otherwise have been provided by the NHS or PSS, it may be appropriate to consider the cost of the time spent providing this care within the NHS and PSS perspective.[228] As such, a scenario analysis is conducted (Section B.3.11.3) in which the costs of unpaid care are included in the analysis.

B.3.2.3 Model structure

A Markov state transition model was developed which characterises patients' progression through AD using 4 distinct health states based on disease severity, replicated in the community and institutional care settings: MCI due to AD, mild AD, moderate AD, and severe AD, and death (9 health states in total) (Figure 31). Health state membership is derived using cohort simulation in discrete time.

Figure 31: Model structure†



Abbreviations: AD – Alzheimer's disease; MCI – mild cognitive impairment.
† Dashed and solid lines are both used to denote possible transitions (dashed lines are used only for legibility where required).

This structure is aligned with previously published Markov models of AD and reflects the impact of progression in disease severity and location of care (i.e., institution or community) in driving HRQoL and cost consequences for patients with AD and their carers.[229–234] Moreover, Markov models were the most commonly used approach among the studies identified by the SLR (Section B.3.1), including the model developed by the Assessment Group for TA217. A Markov model was deemed more suitable than a discrete event simulation (DES), which was used in seven of the 20 studies identified by the SLR, due to the increased computational burden and associated requirement for software other than Excel, and the resulting loss of transparency compared with cohort models. Transparency and ease of validation were identified as important aspects of model design in the conceptual phase of development. These sentiments were echoed by the Assessment Group for TA217, who preferred a Markov model over a DES as the greater data requirements for the latter could not be adequately fulfilled.[235]

B.3.2.3.1 Health state definitions

Model health states are defined by disease severity according to CDR-SB and global CDR, both of which are established clinical assessment of disease severity in AD. CDR-SB has been widely used to define health states in recent economic evaluations (Section B.3.1).[66,236,237] Table 3, Section B.1.3.2 presents how each assessment maps to each stage of AD thus showing how health states are defined.

To align with the primary endpoint of Clarity AD, CDR-SB was used to define health states in the base case. The psychometric properties of CDR-SB, which assesses both cognitive and functional disability (B.2.3.1.1), are particularly useful in early stages of AD and have been in use for more than 20 years in clinical trials in AD and MCI.[238] Global CDR was explored as a scenario as it was identified as a useful assessment of AD progression by clinical experts at the UK HTA advisory board (July 2023), however was not used in the base case due to a lack of natural history data using this assessment (Section B.3.3.1).[61]

B.3.2.3.2 Health state transitions

Patients enter the model in either the 'MCI due to AD' or 'Mild AD' health state. In the base case which evaluates an early AD population, the distribution of patients across these states in the first model cycle is as per the ITT population in Clarity AD (Table 37). It is assumed that all patients enter the model in the community setting, as per Clarity AD.

Patients can transition between all disease severity levels within community and institutional care settings in each cycle, however they cannot return to the community setting once institutionalised. This aligns with published cost-effectiveness studies and clinical expert opinion from a UK HTA advisory board (July 2023) that once institutionalised, patients are unlikely to return to the community if the primary reason for institutionalisation is AD.[61,239,240]

Backwards transitions (i.e., to milder health states) are permitted, as observed in Clarity AD (see Section B.3.3.1.1) and natural history data identified in the SLR (Section B.3.3.1).[241] This was also validated by clinical expert opinion from a UK HTA advisory board (July 2023) which suggested that such improvements are feasible but may only be temporary.[61]

B.3.2.3.3 Cycle length

A one-month cycle length was used to ensure the resource use and associated costs for patients with AD were accurately captured given the bi-weekly lecanemab infusion schedule, and to minimise bias resulting from longer cycle lengths.[242] A one-month cycle length also enables reflection of transient improvements to less severe health states which could not be accurately modelled using longer cycle lengths (e.g. one year), which may overestimate the time spent in improved health states. This

cycle length is also consistent with TA217. Half-cycle correction was implemented using the life-table method.[5]

B.3.2.3.4 Features of the economic analysis

Two NICE appraisals have been conducted in AD. TA111 was a previous appraisal of donepezil, galantamine, rivastigmine and memantine published in 2006. However, the documents for this appraisal are no longer available on the NICE website as the guidance was updated and replaced by TA217 in 2011. In TA217, the Assessment Group detailed key issues identified in TA111 and developed its own economic model, the key features of which are outlined in Table 38 alongside the economic analysis for the current appraisal. Notably, the interventions in TA217 and TA111 were symptomatic rather than disease-modifying treatments, hence the economic analysis focussed on delay in time-to-institutionalisation rather than progression of AD.

Table 38: Features of the economic analysis

Factor	Previous appraisal	Current appraisal	
	TA217[243]	**Chosen values**	**Justification**
Model type	A *de novo* Markov cohort model developed by the EAG identifying key issues in TA111[244]	A *de novo* Markov cohort model	Markov models were used in over half of the UK studies identified in the SLR. Cohort models are typically more transparent than DES models, which are also often associated with high computational burden. In TA217, the committee preferred a Markov approach over a DES approach as the latter required greater data input requirements which could not be suitably informed through UK-specific literature.
Perspective	NHS and PSS	NHS and PSS	Consistent with NICE reference case.
Time horizon	Lifetime	Lifetime	Consistent with NICE reference case.
Cycle length	One-month	One-month	Provides sufficient granularity to capture potential health state transitions and accurately calculate lecanemab costs.
Discount rate	3.5% per year	3.5% per year	Consistent with NICE reference case.
Treatment effect waning	Not reported	[redacted]	[redacted]
Outcome measure	QALYs (EQ-5D)	QALYs (EQ-5D)	Consistent with NICE reference case.
Source of utilities	Jönsson et al, 2006[245]	Clarity AD, Farina et al., 2020[37], and Black et al. 2018.[116]	HRQoL data from Clarity AD for patients (both self-reported and proxy-reported) and caregivers at baseline and every six months were used where possible. However, Clarity AD did

			not contain sufficient observations to inform utility in the moderate AD or severe AD health states and did not collect data on institutionalisation. Therefore, estimates from published literature identified by the SLR were used for these health states. Studies reporting EQ-5D-3L estimates from UK populations were preferred.
Source of drug costs	BNF 2010	BNF 2023	Established source for drug costs within the UK
Source of other costs	• NHS reference costs • PSSRU (latest available) • Dementia UK report 2007	• NHS reference costs • BNF • PSSRU • HCHS	There are established sources of resource use costs within the NHS, and consistent with NICE reference case.

Abbreviations: AD – Alzheimer's disease; BNF – British National Formulary; DES – Discrete event simulation; HCHS – Hospital and community health services; NICE – National Institute for Health and Care Excellence; NHS – National Health Service; PSS – Personal Social Services; PSSRU – Personal Social Services Research Unit; QALY – quality-adjusted life year; UK – United Kingdom

B.3.2.4 Intervention technology and comparators

B.3.2.4.1 Intervention

The final scope defined the intervention as 'lecanemab plus established clinical management' where established clinical management was defined as non-pharmacological management for MCI due to AD, and an AChEI and/or non-pharmacological management for mild AD (current standard of care).[2] This reflects the absence of recommended pharmacologic therapies for MCI due to AD, while the NICE dementia guideline (NG97) recommends AChEIs (donepezil, rivastigmine, and galantamine) and memantine for symptomatic treatment of AD (see Section B.1.3.6.2).[246]

Lecanemab is anticipated to be used alongside AChEIs and non-pharmacological interventions in clinical practice, rather than replace them. This reflects Clarity AD, in which patients were allowed to continue receiving symptomatic AD medication during the study. The costs of AChEIs are therefore included in the economic analysis for lecanemab, in alignment with the final scope.

Non-pharmacological interventions (e.g., cognitive stimulation therapy, group reminiscence therapy, cognitive rehabilitation/occupational therapy, etc.) are not explicitly considered within this analysis for either treatment arm. The outcomes for these interventions are expected to be captured indirectly through health state costs and utility, and their use is expected to be equal in both treatment groups.

Lecanemab is assumed to be administered biweekly at a dose of 10 mg/kg via intravenous (IV) infusion over approximately one hour per Clarity AD and the draft SmPC (Appendix C).

B.3.2.4.2 Comparators

In alignment with the final scope, the comparator considered in the economic analysis is established clinical management as described above, without lecanemab, henceforth referred to as SoC. The comparator consists of symptomatic treatment only as per the intervention. The proportion of patients receiving each symptomatic treatment by health state is summarised in Section B.3.5.2.2.

B.3.3 Clinical parameters and variables

B.3.3.1 AD progression

Clarity AD provides randomised, direct evidence for the comparison of interest and is the study informing the MHRA procedure. Therefore, this was utilised as a primary source of evidence for AD progression in the model. The core study duration was 18 months, and only [redacted]% patients in the placebo arm progressed to moderate AD during the 18-month follow-up. Therefore, a SLR (B.3.3.1.2) conducted to identify

published data on the natural history of AD was used to supplement Clarity AD for the economic analysis.

B.3.3.1.1 Clarity AD

As described above, transition probabilities for the first 18 months of the analysis were calculated from the baseline and 18-month distributions of patients across each health state based on CDR-SB as observed in Clarity AD (Table 39).

As empirical data were available from both arms in Clarity AD, it was possible to estimate transition probabilities for lecanemab and SoC whilst harnessing the benefits of randomisation without the need to parameterise a treatment effect and impose associated structural assumptions, such as limiting the treatment effect to specific transitions. The 18-month transition probabilities derived from Clarity AD were converted to one-month transition probabilities, hence it was assumed the transition probabilities were constant during the first 18 months. Patients who did not complete the core study due to early discontinuation from adverse events, withdrawal of consent, or loss to follow-up did not attend the study visit at month 18, and therefore did not have data imputed and were excluded from the analysis. The proportion of patients who discontinued and were lost to follow-up during the core study was similar between arms (lecanemab: 18.8%, placebo: 15.6% and lecanemab: 0.4%, placebo: 0.6%, respectively).[135]

Of note, the probability of improvement from mild AD to MCI was [redacted]% and [redacted]% for lecanemab and placebo, respectively. Transitions to less severe AD stages were observed in natural history data from the SLR (see Section B.3.3.1). Additionally, clinical expert opinion from the UK HTA advisory board (July 2023) suggested that improvements to less severe health states are possible.[61]

Table 39: Health state occupancy as defined by CDR-SB at month 18

	MCI	Mild AD	Moderate AD	Severe AD
Lecanemab				
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Placebo				
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	MCI	Mild AD	Moderate AD	Severe AD
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AD – Alzheimer's disease; CDR-SB – Clinical dementia rating sum of boxes; FAS+ – Intention-to-treat full analysis; ITT – Intent-to-treat; MCI – mild cognitive impairment.

B.3.3.1.2 Natural history of AD

As described in Section B.3.3.1, a SLR was conducted to identify published natural history data to supplement Clarity AD for the economic analysis. The identification, and selection of published natural history data are described in full in Appendix D.2.1. A total of 40 studies reporting AD transition probabilities were identified through the SLR and were subsequently reviewed to determine their relevance to the decision problem and the economic analysis.

The key criterion for selection of a source of natural history data was a population consisting only of those with confirmed Aβ pathology. [redacted].[2] Patients with Aβ pathology are considered to have a faster rate of disease progression than those without.[247–250] As such, this criterion was necessary to ensure the baseline risk of disease progression in the model is reflective of the target population.[2]

None of the 40 studies identified were specific to the UK. Only three studies reported results for a population with confirmed Aβ pathology (Potashman et al. 2021, Tahami Monfared et al. 2023, and Voss et al. 2023). Tahami Monfared et al. is a simulation model and was therefore excluded. Voss et al. 2023 reports progression from MCI due to AD to dementia due to AD but does not report transitions within dementia due to AD health states. Potashman et al. reports transition probabilities between clinically defined stages of AD across the entire spectrum of disease from MCI due to AD to severe AD, and defines disease stages by CDR-SB, aligning with the health state definitions used in this analysis (Section B.3.2.3.1). Potashman et al. was therefore considered the only appropriate source of natural history data for use in this analysis, in absence of any UK-specific data.[251]

The transition probabilities for disease progression reported in Potashman et al. are based on longitudinal patient-level data for a subset of patients in the National Alzheimer's Coordinating Center (NACC) database with confirmed Aβ pathology. The NACC database is one of the two most commonly used AD databases, having collected data since 2005 and containing longitudinal data from >30 past and present US Alzheimer's Disease research centres for approximately 30,000 patients between 2005-2017, with clinical protocols followed for diagnosis and follow-up. This database is considered a valuable resource for the AD research community and has been used in numerous AD cost-effectiveness analyses in recent years.[252–258]

Additionally, the NACC database was preferred by clinicians in a UK HTA advisory board (July 2023) to the Alzheimer's Disease Neuroimaging Initiative (ADNI) database, another commonly used database in AD, due to concerns regarding the generalisability of the ADNI dataset. These concerns were attributable to selection bias, such as the exclusion of many comorbid conditions.[61]

The progression rates reported by Potashman et al. were estimated through five clinically-defined AD stages: asymptomatic, MCI due to AD, mild AD, moderate AD, severe AD, and death, which were used to inform transition probabilities beyond 18 months in the model.[259] These were generated using multinomial logit regression models predicting an individual's AD stage as a function of AD stage at the previous visit and adjusted for covariates including time between initial and follow-up visits, age, sex, years of education, and concomitant symptomatic AD medication use.

The transitions reported by Potashman et al. from MCI due to AD to more severe states were structured as an annual probability of progression and a subsequent 'landing spot', dictating which health state patients transitioned to (Table 40). Of the 23.2% of individuals progressing annually from MCI due to AD to mild or moderate AD, 72.7% transitioned to mild AD and 27.3% to moderate AD. Annual transition probabilities from Potashman et al. were transformed to monthly probabilities for the economic analysis by taking the 12th root of the transition matrix, computed via the eigen decomposition method using the EXPM package in R (Table 41).[260]

Table 40: Annual transition probabilities from MCI due to AD

Input	Value	Source
Annual probability of progression from MCI	23.2%	Potashman et al.[203]
'Landing spot' distribution		
Mild AD	72.7%	Potashman et al.[203]
Moderate AD	27.3%	
Severe AD	0.0%	

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

Table 41: Annual transition probabilities across dementia states

	To MCI	To Mild AD	To Moderate AD	To Severe AD	Source
From Mild AD	3.3%	57.1%	35.2%	4.4%	Potashman et al.[203]
From Moderate AD	0.0%	2.9%	55.1%	42.0%	
From Severe AD	0.0%	0.0%	1.9%	98.1%	

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

B.3.3.1.3 Treatment effect of lecanemab

As discussed in Section B.3.3.1.1, transition probabilities for the first 18 months of the analysis were calculated from the distribution of patients across each health state based on CDR-SB as observed in Clarity AD. Therefore, the parameterisation of a treatment effect during this period was not required.

Beyond 18 months, an estimate of treatment effect for lecanemab vs. SoC which could be applied to the transition probabilities from Potashman et al. was required. For consistency with Clarity AD, the same analysis that was conducted for the exploratory endpoint of time to worsening of Global CDR score at 18 months, with worsening defined as progression from MCI due to AD to mild AD, or from mild AD to moderate AD, was used for CDR-SB. The output of the Global CDR analysis was a hazard ratio for disease progression for lecanemab vs. placebo (0.69, Section B.2.6.4), estimated using a Cox proportional hazards model. To align with the model structure and health state definitions used in the base case, this analysis was conducted separately for patients starting in MCI due to AD and mild AD and time to worsening is defined as time in days from randomisation to a confirmed worsening of the CDR-SB scores to the next health state (treated as 'confirmed' when a worsening is observed in two consecutive visits). Times were censored at the date of last CDR assessment if no event was observed.

Modelling the effect of lecanemab on AD progression via a hazard ratio was deemed appropriate for the economic analysis as this is based on all available patients at risk of transition and uses all available data, censoring patients that have not had an event. Each model included treatment group and Clarity AD study strata clinical subgroup, use of AD symptomatic medication at baseline, *APOE4* carrier status, and region as covariates.

Time to worsening based on CDR-SB for the MCI due to AD and mild AD populations in Clarity AD are presented in Figure 32 and Figure 33, respectively. Overall, 188 patients in the lecanemab arm experienced a worsening event (21.9%), compared to 252 in the placebo arm (28.8%). The hazard ratios based on CDR-SB were [redacted] (95% CI: [redacted]; *p*=[redacted]) and [redacted] (95% CI: [redacted]; *p*=[redacted]) for the MCI due to AD and mild AD populations, respectively. The proportional hazards assumption was assessed via testing for time-dependent covariates based on the interaction of each factor in the model and time. All tests showed p-values of >0.05 (CDR-SB overall, *p*= [redacted]; MCI, [redacted]; mild AD, *p*=[redacted]), indicating the proportional hazard assumption holds.

A corresponding analysis was also performed for global CDR, which estimated hazard ratios of [redacted] and [redacted] for the MCI and mild AD populations, respectively. The hazard ratios based on global CDR are used in the scenario analysis where global CDR is used to define the model health states (Section B.3.11.3).

Figure 32: Kaplan-Meier curve for time to worsening of CDR-SB (MCI) – ITT FAS+

Abbreviations: CDR-SB – Clinical dementia rating sum of boxes; MCI – mild cognitive impairment.
Source: Data on file[261]

Figure 33: Kaplan-Meier curve for time to worsening of CDR-SB (Mild AD) – ITT FAS+

Abbreviations: AD – Alzheimer's disease; CDR-SB – Clinical dementia rating sum of boxes
Source: Data on file[261]

In the base case analysis, the lecanemab treatment effect is assumed constant for as long as patients remain on treatment and for those who discontinue due to all-cause discontinuation, given hazard ratios were estimated under the ITT principle and therefore implicitly reflect the impact of such discontinuations (Section B.3.3.1.3). Treatment effect assumptions relating to stopping rules which may be applied in clinical practice are discussed in Section B.3.3.3.

B.3.3.2 All-cause treatment discontinuation

The rate of all-cause discontinuation in Clarity AD was relatively constant (Figure 34), hence is modelled as a constant rate. The rate of discontinuation in the lecanemab arm was calculated to be [redacted]% per year (95% CI: [redacted]) from the total number of discontinuation events (n=[redacted]) divided by the total cumulative exposure time to lecanemab ([redacted] patient-years). This provided a monthly rate of all-cause discontinuation of [redacted]% for lecanemab.

Figure 34: Kaplan-Meier curves for time to discontinuation of study treatment in Clarity AD

Note: For patients who completed study treatment at month 18, the time to discontinuation of study treatment was censored at last infusion date in the core study.
Abbreviations: AD - Alzheimer's disease.

B.3.3.3 Treatment stopping rules

Clarity AD did not include a treatment stopping rule for lecanemab. The draft SmPC for lecanemab states [redacted](Appendix C).[20] Currently, there is no consensus among UK clinical experts regarding exactly which stopping rule(s) will be applied in clinical practice, however options have been proposed including based on amyloid clearance or amyloid negativity.[61] This feedback has also been shared with NHS England and it is expected that discussions regarding a stopping rule for lecanemab in NHS practice will continue in parallel to this appraisal. The associated economic modelling will therefore be submitted at an appropriate milestone (e.g. technical engagement).

The current economic analysis includes stopping rules for progression to moderate AD and entering institutional care, to reflect UK clinical expert opinion.[61]The rationale for these stopping rules and the associated assumptions regarding the lecanemab treatment effect is explained in further detail below.

B.3.3.3.1 Disease severity

Clarity AD included patients with MCI due to AD or mild AD (the anticipated positioning of lecanemab) and the draft SmPC for lecanemab states [redacted] (Appendix C).[20] Clinical expert feedback at a UK HTA advisory board (July 2023) was that the overriding principal of deciding when to stop treatment should be to prolong patients time in earlier stages of disease, where they remain independent and have better quality of life.[61] In the Institute for Clinical Economic Review (ICER) assessment of lecanemab, it was assumed that people stop treatment upon progression to moderate AD, due to the absence of data from Clarity AD.[262]

As such, patients are assumed to discontinue treatment upon progression to moderate AD in the base case analysis. [redacted]

B.3.3.3.2 Institutionalisation

Consensus among UK clinical experts at the July 2023 advisory board was that patients would not be treated with a DMT once they had been institutionalised.[61] As such, this was implemented in the base case analysis regardless of disease severity. As initiation of institutional care is dependent on factors unrelated to the patient's disease progression, such as availability of informal care, having a non-spousal informal caregiver or a caregiver that does not live with the patient, and ability of the informal caregiver to care for the patient, transition probabilities for lecanemab versus SoC patients discontinuing treatment due to institutionalisation are as per Section B.3.3.1.3 and B.3.3.3.1.[239,263,264]

B.3.3.4 Risk of institutionalisation

Data for the rate of institutionalisation were not available from Clarity AD and data identified through the natural history SLR were sparse, as this search was primarily focussed on identifying transition probabilities between health states based on disease severity rather than care setting. All four studies that reported a risk of institutionalisation (Appendix D) were US-based, and none reported institutionalisation in an amyloid positive population.[253,255,256,265]

As such, an additional hand search for studies reporting rates of institutionalisation in AD was conducted. No studies were identified which reported data in an amyloid

positive population, however two UK sources were identified. Knapp et al. 2016[204] is a patient registry analysis of 3,075 UK-based individuals with AD, and Belger et al. 2019[239] (GERAS study) is a prospective, non-interventional cohort study in patients with AD in three European countries (France, Germany, and UK), comprising 1,495 patients. Both studies reported risk of institutionalisation by AD severity according to MMSE.[204,239]

Knapp et al.[204] was selected for the base case analysis as it reports risk of institutionalisation specific to the UK based on larger sample than Belger et al.[239] The study reports six-month probabilities of admission to an institution whilst in mild AD, moderate AD, and severe AD (Table 42). These were converted to monthly probabilities to align with the model cycle length. At the start of the first six-month study period the distribution of individuals was 44.3% experiencing mild dementia, 45.2% moderate dementia, and 10.5% severe dementia.[204] The probability of transitioning to institutionalised care increases with increasing severity of disease.

In the absence of data reported by Knapp et al.,[204] individuals in the MCI due to AD health state are assumed to have no risk of institutionalisation, given the associated risk for patients in mild AD is very low (0.51%). This aligns with other studies which report no risk within the MCI health state, and with consensus among UK clinicians at the UK HTA advisory board (July 2023) that patients with MCI due to AD would not be institutionalised.[61,239,256]

Belger et al.[239] was used in a scenario analysis. The study reports 3-year probabilities of admission to an institution whilst in mild AD, moderate AD, and severe AD, which were converted to monthly probabilities to align with the model cycle length (Table 42). The probability of transitioning to institutionalised care increases with increasing severity of disease, consistent with Knapp et al.[204]

Table 42: Probability of institutionalisation

Model health state	Knapp et al. 2016[204]		Belger et al. 2019[239]	
	6-month probability	Monthly probability (base case)	3-year probability	Monthly probability (scenario)
MCI due to AD	0%	0%	0%	0%
Mild AD	3.00%	0.51%	15.6%	0.43%
Moderate AD	8.00%	1.38%	29.5%	0.82%
Severe AD	10.00%	1.74%	32.5%	0.90%

Source: Knapp et al.[204]
Abbreviations: AD – Alzheimer's disease; MCI – Mild cognitive disorder

B.3.3.5 Mortality

There were only 15 deaths in Clarity AD (0.8% of ITT population), therefore transitions to death were informed by UK general population life tables, adjusted for excess mortality associated with AD taken from published sources identified in the literature (described in Section B.3.3.1.2).

The model structure required mortality estimates for MCI due to AD, mild, moderate, and severe AD health states defined using CDR-SB. In addition, effects estimated relative to general population mortality were preferred to those on the absolute scale, to enable modelling of the increasing risk of mortality with age experienced by AD patients over lifetime. Finally, studies reporting data for a population with confirmed Aβ pathology were preferred for consistency with the source of transition probabilities for AD progression and the decision problem for this appraisal.

None of the natural history studies identified through the SLR met the criteria described above, therefore additional hand searches were conducted.

Eight studies reporting AD-specific mortality were identified via hand searches, four of which reported relative mortality rates and the remaining four reported absolute risks.[253,255,266,267] Only one study (Crowell et al.) reported relative mortality rates based on NACC data, which includes patients with confirmed Aβ pathology, and was therefore used in the base case analysis.[205]

Crowell et al. report hazard ratios of death across all stages of AD compared with cognitively normal participants, using a Cox proportional-hazards models adjusting for age, sex, and other variables.[205] The study was based on 12,414 US patients with a mean age of 70.8 years (SD = 9.14) from the Uniform Data Set of the NACC with 15 years of follow-up from 2005-2021.[268] Participants had annual follow-up visits until death (or dropout) and were censored upon progression to another stage of AD, while adding observation time to the new stage of AD.

Relative risks from 'model 2' reported by Crowell et al. were selected for the base case as this model included adjustment for age and sex, as well as years of education; although years of education is not considered in the economic model. This model estimates a decreased risk of death in the MCI due to AD subgroup (HR 0.63, 95% CI: 0.46, 0.88) compared with the cognitively normal group. Corresponding HRs for the mild AD, moderate AD, and severe AD were 2.43 (95% CI: 1.81, 3.26), 3.77 (95% CI: 2.66, 5.34), and 8.53 (95% CI: 5.45, 13.3), respectively.[205]

The relative effect of mortality was applied to the age- and sex-adjusted estimates of general population mortality, using the Office for National Statistics 2022/2023 life tables for England and Wales.[269] Mortality is applied as the sex-weighted annual mortality adjusted to the monthly cycle length. Table 43 reports the relative risks according to model health state.

Table 43: Mortality hazard ratio by disease state

Health state	Hazard ratio
MCI due to AD	0.63
Mild AD	2.43
Moderate AD	3.77
Severe AD	8.53

Abbreviations: AD, Alzheimer's disease; MCI, mild cognitive impairment.
Source: Crowell et al.[205]

B.3.3.6 Adverse reactions

The criteria for selecting adverse events for inclusion in the analysis were as follows:

- Treatment-related incidence of grade 3+ AEs occurring in ≥5% patients in either treatment arm of Clarity AD, as is standard practice in HTAs.
- ARIA-E, ARIA-H, and infusion-related reactions irrespective of incidence and severity, given these are AEs of special interest (AESIs).

Other than the AESIs outlined above, no grade 3+ treatment-related AEs occurred in ≥5% patients in either arm of Clarity AD. As such, the only AEs that met the criteria for inclusion in the analysis were ARIA-E, ARIA-H, and infusion-related reactions.

AE rates were modelled by severity as per Section B.2.10.4 but not by presence of symptoms to reflect the associated appropriate use recommendations reported by Cummings et al. Rates of isolated ARIA-H were used to avoid double-counting given this can occur concurrently with ARIA-E (Section B.2.3.1.2) and treatment-emergent rates were used given the natural occurrence of ARIA-H in AD patients. As adverse event frequencies are provided for the duration of Clarity AD, the 18-month AE costs are applied in the first cycle only. The rate of infusion-related reactions for standard of care was assumed to be 0% given these patients will not receive a placebo infusion in clinical practice.

Further detail on the economic impact of these AEs can be found in Section B.3.5.5.

Table 44: Adverse event frequencies

Event	Severity*	Lecanemab	SoC	Source
Infusion-related reaction	Mild	[redacted]	[redacted]	Section B.2.10.4.3
	Moderate	[redacted]	[redacted]	
	Severe	[redacted]	[redacted]	
	Serious	[redacted]	[redacted]	
ARIA-E	Mild	[redacted]	[redacted]	Section B.2.10.4.1
	Moderate	[redacted]	[redacted]	
	Severe	[redacted]	[redacted]	
	Serious	[redacted]	[redacted]	

ARIA-H	Mild	[redacted]	[redacted]	Section B.2.10.4.2
	Moderate	[redacted]	[redacted]	
	Severe	[redacted]	[redacted]	
	Serious	[redacted]	[redacted]	

Source: Clarity AD[135]
Abbreviations: AE – Adverse event; ARIA-E – amyloid-related imaging abnormality-oedema/effusion; ARIA-H – amyloid-related imaging abnormality-microhaemorrhage and haemosiderin deposit
*ARIA-E and ARIA-H based on maximum radiographic severity. Infusion-related reactions are based on NCI-CTCAE criteria; mild = grade 1, moderate = grade 2, severe = grade 3, serious = grade 4

B.3.4 Measurement and valuation of health effects

B.3.4.1 Health-related quality of life data from clinical trials

In Clarity AD, patients' HRQoL was measured using EQ-5D-5L, QOL-AD, and ZBI at baseline and every six months (Section B.2.6.5). Results for some of these patient-reported outcomes including the EQ-5D VAS have been published.[1,2] To validate the responses provided by patients, the patient's study partner served as the patient's proxy and completed the EQ-5D-5L and QOL-AD on the patient's behalf, in addition to their own EQ-5D-5L. Additionally, every six months, the study partner burden was measured using ZBI to assess the stresses experienced by study partners of patients with early AD (Section B.2.6.5).

B.3.4.1.1 EQ-5D-3L index scores

To inform the economic analysis, EQ-5D-5L data from Clarity AD were mapped to EQ-5D-3L index scores using the algorithm reported by Hernandez Alava et al., in line with recommendations from the NICE DSU.[270] All available data were pooled based on health state membership and study arm, and mean estimates of utility index score calculated. No imputation of missing data was performed. This was conducted separately for patient-reported, patient-by-proxy and caregiver-reported data.

The resulting EQ-5D-3L index scores are high relative to the age- and sex- matched general population (Table 45); Hernández Alava et al. report scores for the general population aged 70 of between 0.760 and 0.841, which are lower than the mean values observed across the MCI due to AD health state. This observation is consistent with findings within the literature (Section B.3.4.3). Differences in mean EQ-5D-3L index score between study arms were observed for the MCI due to AD and mild AD health states (which contained 98% of all observations), which may reflect a HRQoL benefit for lecanemab independent from differences in disease progression via CDR-SB.

Table 45: Summary of EQ-5D Utility Index Score by Health State Using CDR-SB Score (Clarity AD, ITT FAS+)

Health state		Patient-reported		Patient-by-proxy		Caregiver	
		Lecanemab	Placebo	Lecanemab	Placebo	Lecanemab	Placebo
MCI due to AD	n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mild AD	n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Moderate AD	n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Severe AD	n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AD – Alzheimer's Disease; MCI – mild cognitive impairment; SD – standard deviation; n –number of observations

B.3.4.2 Mapping

Mapping QOL-AD data from Clarity AD to EQ-5D was explored as QOL-AD is considered more sensitive than EQ-5D-5L when assessing QoL in AD patients.[271] A hand search for a mapping algorithm from QOL-AD to EQ-5D identified only one publication, Rombach et al.[271] which described mapping attempting to predict the probability of response to each level for each item of the EQ-5D-5L, therefore not directly predicting EQ-5D score. The model coefficients were not reported in the paper, nor was the Stata code developed by the authors to conduct the mapping. As such, this mapping algorithm could not be used. As no other publications were identified, it was not possible to map from QOL-AD to EQ-5D using a published mapping algorithm.

B.3.4.3 Health-related quality of life studies

An SLR was conducted to identify studies reporting the impact of all stages of AD, including MCI due to AD and mild, moderate, and severe AD, on the HRQoL of patients and caregivers, with specific focus on identifying health state utilities. Full details of the SLR strategy, study selection process, and results are presented in Appendix H.

B.3.4.3.1 Patient HRQoL (self-reported and by-proxy)

The SLR identified 19 UK-specific studies reporting utility values. Of the 19 studies identified, 14 reported patient-reported utilities and 13 studies reported patient-by-proxy EQ-5D values. Six of the 19 studies reported EQ-5D utilities for UK patients across various dementia severity levels. In general, instances where both patient-reported and patient-by-proxy-rated utilities were reported indicated that patient-by-proxy-rated utilities tended to be lower than patients' self-reported utilities. In addition, the SLR found one meta-analysis reporting data from multiple countries, Landeiro et al. (2020), which meta-analysed EQ-5D utility estimates from 48 studies identified via an SLR.[95]

- Coucill et al. (2001) reported self-reported EQ-5D values grouped for the combined questionable dementia (MCI)/mild dementia group (0.86) and the moderate dementia group (0.72); the dementia type in this study was mixed.

- Bryan et al. (2005) reported patient-by-proxy-rated EQ-5D values for patients, grouped for the combined questionable dementia (MCI)/mild dementia group (0.57) and moderate dementia group (0.61); the dementia type in this study was mixed.

- Wimo et al. (2013) reported patient-by-proxy-rated EQ-5D index values of 0.68, 0.65, and 0.48 for mild, moderate, and moderately severe-severe AD levels, respectively.

- Ortega et al. (2015) reported self-rated and patient-by-proxy-rated EQ-5D values, respectively, for mild dementia (0.79/0.63) and moderate dementia due to mixed causes (0.72/0.52).

- Mulhern et al. (2013) reported self-reported and patient-by-proxy-rated EQ-5D values, respectively, for mild dementia (0.71/0.57), moderate dementia (0.69/0.47), and severe dementia due to AD (0.67/0.43); all patients also had depression.

- Farina et al. (2020) reported self-reported and patient-by-proxy-reported utilities for mild, moderate, and severe dementia (note that the dementia type in this study was mixed). Self-reported and proxy-reported EQ-5D values were 0.80/0.70 for mild dementia and 0.80/0.50 for moderate dementia, and not reported/0.40 for severe dementia.

Three studies reported patient utility values for MCI (termed questionable dementia in the studies). Notably, two of these studies consolidated the reporting of utility values for the MCI and mild dementia states together rather than for MCI alone (Coucill 2001, Bryan 2005). A specific definition for MCI was lacking in one study, Park 2017, which reported patient and proxy-reported EQ-5D utility values of 0.70

and 0.68, respectively.

Farina et al. (2020) reported on disparities in patient utilities between community and institutional care. Using a regression model, the study estimated the effect of institutionalisation, specifically residential care home settings, on EQ-5D. The findings indicated a significant association between residing in a care home and diminished quality of life, with a notable 0.13 utility decrement observed in EQ-5D proxy-reported outcomes. However, Farina et al. did not report decrements based on disease severity levels.

B.3.4.3.2 Caregiver HRQoL

Eight studies reported caregiver self-reported utilities (Woods et al. 2012, Bradshaw et al. 2013, Bleijlevens et al. 2015, Black et al. 2018, Handels et al. 2018, Dixit et al. 2020, Farina et al. 2020, Fang et al. 2016). Of these, three studies reported caregiver EQ-5D utilities by various dementia severity levels.

- Fang et al. (2016) compared utilities of UK and Canadian AD patients and their caregivers across mild and moderate AD severity. UK-based median caregiver EQ-5D utilities for mild AD was 0.81 and moderate AD was 0.80.
- Farina et al. (2020) reported mean caregiver EQ-5D data for caring for patients with mild (0.8), moderate (0.8) and severe (0.9) AD respectively.
- Black et al. (2018) provided caregiver EQ-5D utilities for caring for patients with prodromal AD (0.896), mild AD (0.886), moderate AD (0.862) and severe AD (0.807).

Fang et al. (2016) did not report utility values for severe AD. Farina et al. (2020) is the only exclusively UK study, however the mean carer utility value for severe AD lacked face validity as it exceeds age- and sex-matched general population utility. Black et al. (2018) reported mean EQ-5D data for caregivers by disease stage (for the person with dementia). This study applied country-specific tariffs with results aggregated across the whole sample. In regression analyses, the study reported a statistically significant reduction in EQ-5D values for caregivers of people with moderate dementia due to AD and severe dementia due to AD (-0.033).

Additionally, the SLR identified a further three non-UK studies reporting caregiver self-reported utilities by AD health state: Van Hezik-Wester et al. 2023, Lopez-Bastida et al. 2006, and Mesterton et al. 2010.[36,272,273]

B.3.4.4 HRQoL data used in the cost-effectiveness analysis

The model structure (Section B.3.2.3) requires health state utilities for MCI due to AD, mild, moderate and severe AD, stratified by care setting (community vs institution) for patient and caregiver. The effect of lecanemab, including due to AEs, must also be considered.

However, Clarity AD did not contain sufficient observations to inform health state utilities for moderate or severe AD due to the small number of patients progressing to moderate AD during the 18-month follow-up period (Table 45), and did not collect data for the institutional care setting. Therefore, patient and caregiver utility estimates from published studies were required for moderate and severe AD in the community and all institutional care health states. To preserve differences between health states when using published utilities, decrements were calculated for each set of published utilities relative to the previous health state and applied additively in the economic analysis to the associated utility from Clarity AD. Therefore, a key requirement of published studies was reporting of health state utilities for mild AD, as well as moderate and severe AD, to enable decrements to be derived. Studies reporting EQ-5D-3L utilities from exclusively UK respondents, stratified by care setting, were preferred to align with the NICE reference case and model health states.

B.3.4.4.1 Patient utilities

To reflect the NICE reference case and given its relevance to the decision problem, data from Clarity AD were used where possible. However, as described above, the study did not provide sufficient observations to inform health state utilities for moderate or severe AD and did not collect data for the institutional setting, hence the SLR was consulted for alternative estimates for these states.

In addition, patient-reported and patient-by-proxy reported EQ-5D scores diverge substantially as AD severity increases. Landeiro et al. meta-analysed EQ-5D utility estimates from 48 studies identified via a SLR and observed that people with severe AD still reported relatively high utilities (weighted mean 0.82; 95% CI: 0.64, 1.00), whereas patient-by-proxy utilities suggested QoL was much lower (weighted mean 0.36; 95% CI: 0.18, 0.53).[95] The TA217 Assessment Group also noted that patients self-report much higher utility values compared to proxy-estimates by their carers.[243] In a UK HTA advisory board (July 2023), three clinicians advised that it would be appropriate to switch from patient-reported utilities to patient-by-proxy utilities in later stages of AD.[61] One clinician stated that it would be appropriate to switch at moderate AD and another suggested severe AD since the patient is less able to respond. Therefore, the base case analysis used patient-reported estimates for MCI due to AD and mild AD and proxy-reported estimates for moderate and severe AD health state utilities for patients. The specific data used are described in subsequent sections.

B.3.4.4.1.1 Community care

In the base-case, patient-reported, treatment-specific, mean EQ-5D-3L index scores based on Clarity AD were used for MCI due to AD and mild AD health state utilities (Table 45). It was assumed the estimates for lecanemab implicitly reflect the HRQoL impact of adverse events and therefore explicit modelling of this was not required.

For moderate and severe AD health states, published subject by proxy estimates were obtained from the SLR. Of the studies identified, only three were UK-based and reported utilities estimates for the health states of interest.[37,274,275] Farina et al. was selected for the base case analysis, as it reports EQ-5D-3L by-proxy estimates for all AD health states, defined using the standardised MMSE from carers of 307 participants in the MODEM study, recruited from memory services in Sussex, UK, or self-referral from a national electronic database, community groups and care homes in the south-east of England. The associated utility estimates are 0.5 (SD=0.3) and 0.4 (SD=0.3) for moderate AD and severe AD, respectively.

Of the remaining 2 studies, Mulhern et al. report estimates for a population with dementia (possible or probable AD) and depression, hence this study was dismissed due to heterogeneity of the population. Second, Wimo et al. reported estimates with moderately-severe and severe pooled together using an MMSE cutoff for this state of 15 rather than 10 as standard, hence this study was dismissed given the health state definitions did not align with the economic model.

As a scenario analysis, utilities for all health states were taken from Landeiro et al. which meta-analysed EQ-5D utility estimates from 48 studies identified via an SLR.[95] Whilst these data include ex-UK studies, and therefore weren't considered for the base case, they provide health state utility estimates from a large sample of AD patients.

B.3.4.4.1.2 Institutional care

The HRQoL impact of patients residing in an institution rather than the community is modelled based on Farina et al. for the same reasons as described for the community health state utilities. Coefficients for the care home residential setting of -0.01 (95% CI: -0.12, 0.11) and -0.16 (95% CI: -0.23, -0.03) from patient-reported and proxy-reported EQ-5D-3L regression models were applied additively to the MCI due to AD/mild AD and moderate/severe AD community care health state utilities respectively.

B.3.4.4.2 Caregiver utilities

Most patients with AD require assistance from an unpaid carer to support their day-to-day activities.[276] Amongst these carers, 80% have reported less time for social activities, and 75% reported a decrease or cessation of their leisure activities including hobbies and travel.[277] Approximately 95% of carers have reported a negative impact on their mental or physical health.[278] Therefore, caregiver utilities are included in the economic analysis to capture the associated burden of AD.

The most appropriate method to apply caregiver utility in cost-effectiveness analysis is not well defined. The NICE health technology evaluation manual recommends that evaluations should consider all health effects, including carers when relevant, without detailing a preference for a specific approach.[200] In a review of the application of carer HRQoL in NICE appraisals, Pennington et al. found that 11 of 16

appraisals used utility decrements for carers, modelled as a function of the patient's health state.[279] This approach was used in the base-case analysis, with decrements relative to the MCI health state being applied in more severe health states. Whilst commonly used, this approach has the undesirable property that if a patient dies, the decrement ceases to be incurred, and therefore this will tend to disadvantage treatments which extend life. As detailed by Pennington et al., this assumption is not consistent with patients' and carers' preferences and raises the issue of how QALYs accruing to patients and carers should be valued where an intervention may lead to gains for one and a loss for the other.[279]

Therefore, a scenario analysis is presented in which caregiver utility is modelled as the absolute QoL for both caregivers and patients summed in each cycle, as reported by Large.[280] This approach includes caregivers as separate entities, with quality of life included using the absolute utility based on the health state that the patient resides. No further QALYs were assumed to accrue following death, which avoids the paradoxical scenario in which the death of patients may be associated with an improvement in quality of life in the model.

B.3.4.4.2.1 Community care

In the base case analysis, caregiver utilities from Clarity AD were used for the MCI due to AD and mild AD health states to align with patient health state utilities (Table 45). For moderate and severe AD, the SLR was consulted for UK studies reporting EQ-5D-3L utilities that could be used to derive utility decrements for these health states. Farina et al. was the only exclusively UK study, however the severe AD carer estimate (0.9) did not have face validity as it exceeds age- and sex- matched general population utility.

Therefore, non-UK studies identified by the SLR were considered. Four non-UK studies were identified, three of which were included in the economic analysis (Table 46). Van Hezik-Wester et al. was dismissed as it reported counterintuitive EQ-5D-5L estimates (higher utility for severe than moderate AD) elicited from Dutch respondents via an online vignette survey.

Of the remaining three studies, Black et al. reported EQ-5D-3L decrements from a regression analysis based on data from a large cross-sectional survey of physicians, their consulting patients, and caregivers conducted in France, Germany, Italy, Spain, UK, and the US. Health states were defined by MMSE using established thresholds. This study was used in the base case analysis given it included UK patients. Lopez-Bastida et al. and Mesterton et al., which report EQ-5D-3L estimates for Spanish and Swedish populations, respectively, with health states defined by CDR Global and MMSE, respectively, were used in scenario analyses.

Table 46: Caregiver utility data from published literature

Health state	Black et al.[116]	Lopez-Bastida et al.[272]	Mesterton et al.*[36]
Mild AD	-0.018	0.71	0.80
Moderate AD	-0.033 (-0.033)	0.66 (-0.05)	0.77 (-0.03)
Severe AD	-0.020 (-0.053)	0.64 (-0.07)	0.75 (-0.05)

All decrements in brackets are vs. mild AD. *Values obtained from Figure 1 in publication.
Abbreviations – AD – Alzheimer's disease

B.3.4.4.2.1 Institutional care

To align with patient health state utilities and capture the impact of the patient's care setting on the caregiver's HRQoL, the coefficient from Farina et al. for the care home residential setting from the caregiver EQ-5D-3L regression model of -0.09 (95% CI: -0.13, 0.03) was applied additively to the community care utilities in all health states.

B.3.5 Cost and healthcare resource use identification, measurement, and valuation

A SLR was conducted to identify studies reporting cost and healthcare resource use (HCRU) data associated with AD in the UK. Full details of the SLR are provided in Appendix I. The SLR was conducted iteratively, with the original SLR conducted in 2017 and four SLR updates conducted up until August 2023 (Table 47).

Table 47: Summary of the HCRU SLRs conducted to date

Year of search	2023 (current)	2021	2020	2018	2017
Search dates	27th June 2021 to 31st August 2023	30th March 2020 to 27th June 2021	1st November 2018 to 30th March 2020	1st January 2017 to 6th December 2018	1st January 2000 to 4th May 2017

The SLR identified 26 studies across 32 publications that reported costs and HCRU data relevant to both pharmacological and non-pharmacological interventions for the healthcare setting in the UK. The studies covered a period of 19 years from 1990 to 2019. The GERAS study, an observational study which reported resource use and costs associated with AD for patients in the UK, France and Germany, comprised of seven publications.[38,119,120,122,239,281,282]

Three publication reported cost and HCRU in mild dementia, seven publications in mild to moderate dementia, two publications in moderate to severe dementia, and one publication in normal to severe dementia. Five publications reported cost and HCRU for each AD severity across mild, moderate, and severe AD (including

moderately severe/severe AD). One publication reported HCRU in MCI in addition to mild, moderate, and severe AD, and one publication estimated the impact of AD on public finances of patients with a diagnosis of MCI due to AD to death. The remaining 12 publications did not specify of dementia or AD.

Ten publications reported on both institutional and community care, whilst 15 considered patients living in a community setting only, and three in an institutional setting. One publication assessed risk and cost of admission to institutional care in those receiving community care at the initial time of assessment. Three publications did not specify the care setting.

Costs and resource use categories reported in the studies varied, including resource utilisation such as healthcare expenses (day visits, overnight stays, A&E visits, and medication costs), community healthcare expenses (social assistance, mental health aid, equipment and adjustments, professional caregiver assistance), and costs associated with informal unpaid care and support. Seven publications reported caregiver resource use, including the time spent by caregivers.

Seven publications considered how disease severity influences the costs and/or HCRU among those with dementia due to AD. All these studies consistently indicated that both costs and HCRU rise in tandem with the progression of disease severity, across various aspects of HCRU including medical consultations, hours of professional caregiving, general hospital inpatient care, mental health inpatient care, institutionalisation, social care, and societal costs. Four publications reported HCRU from a payer perspective, three from a societal perspective, and one publication (Paquete et al. 2022) reported both healthcare and formal social care costs. Paquete et al. was the only study to report costs across all disease severities and for both community and institution settings. However, although Paquete et al. presented health state costs for the MCI state, the costs presented were sourced from an Alzheimer's Society 2014 report (inflated to the 2019/20 cost year), which does not report costs for the MCI health state. As such, Paquete et al. used the ratio of care costs between MCI due to AD and mild dementia due to AD reported by Robinson et al. and applied this ratio to the mild AD costs to derive costs for the MCI state.[109,283] As the health state costs reported in Paquete et al. were inflated from the original values and the inflation indices used was not specified, the original values were sought from the Alzheimer's Society 2014 report. This report was not identified in the original SLR as it is not a peer-reviewed journal article nor a conference abstract, therefore did not meet the PICOS criteria for publication type.

In light of this, an additional hand search was conducted to identify additional sources of health state costs for the model reporting direct and non-direct medical costs classified according to severity and setting for UK patients with dementia due to AD. One additional paper was identified that met these criteria, Gustavsson et al. 2011. Further details of these studies are presented in Section B.3.5.3.

B.3.5.1 Costs included in the model

This analysis includes the costs associated with acquisition, administration, monitoring, diagnostic testing, symptomatic treatment, adverse events, and direct medical and direct non-medical care (i.e. social care costs met by local authorities). As discussed in Section B.3.2.2, a scenario analysis is presented to capture the cost of time spent by family members, friends, and partners to provide unpaid care to patients with AD, which might otherwise have been provided by the NHS or PSS, in line with the NICE methods manual for health technology evaluations.[5]

Where possible, published sources of unit costs, such as NHS Reference Costs 2021/22,[284] Drugs and Pharmaceutical electronic market information tool (eMIT), the British National Formulary (BNF), and Personal Social Services Research Unit (PSSRU) were used. When necessary, costs were inflated to 2023 using the hospital and community health services (HCHS) pay and prices index from the Unit Costs of Health and Social Care, as issued by the PSSRU.[285]

B.3.5.2 Intervention and comparators' costs and resource use

B.3.5.2.1 Drug acquisition

The monthly cost of lecanemab is calculated using the unit cost of each vial, the number of vials required per infusion, and the number of infusions per month. The list price of each vial is subject to DHSC approval (Table 48). [redacted].

Table 48: Lecanemab drug acquisition cost

Vial size	Cost per vial	Source
200mg	[redacted]	Eisai data on file, subject to DHSC approval
500mg	[redacted]	

Abbreviations: mg – milligram.

The lecanemab dosing regimen is 10mg/kg intravenous infusion once every two weeks (equating to 2.17 doses per month). Optimal (lowest cost) combinations of vials were calculated for 10kg weight bands covering the weight distribution in Clarity AD using the method of moments, allowing for the incorporation of vial wastage (Table 49). To reflect the UK population as closely as possible, the weight distribution of the European ITT population (n=390) of Clarity AD was used for the weight distribution. The associated mean weight was [redacted]). Table 49 reports the optimal vials for each weight band and the resulting total cost per dose.

Mean compliance for lecanemab was informed by Clarity AD ([redacted]), defined as: (total number of infusions patients actually received) / (total number of infusions the patients could have received), regardless of infusion interruption.[136] The monthly acquisition cost including non-compliance is [redacted].

Table 49: Lecanemab costs per administration

Weight band (kg)	Proportion of patients	200mg	500mg	Total cost
≤ 40 kg	[redacted]	[redacted]	[redacted]	[redacted]
> 40 x ≤ 50 kg	[redacted]	[redacted]	[redacted]	[redacted]
> 50 to ≤ 60 kg	[redacted]	[redacted]	[redacted]	[redacted]
> 60 to ≤ 70 kg	[redacted]	[redacted]	[redacted]	[redacted]
> 70 to ≤ 80 kg	[redacted]	[redacted]	[redacted]	[redacted]
> 80 to ≤ 90 kg	[redacted]	[redacted]	[redacted]	[redacted]
> 90 to ≤ 100 kg	[redacted]	[redacted]	[redacted]	[redacted]
> 100 to ≤ 110kg	[redacted]	[redacted]	[redacted]	[redacted]
> 110kg	[redacted]	[redacted]	[redacted]	[redacted]
Weighted total (100% compliance)				[redacted]
Weighted total (including non-compliance)				[redacted]

Abbreviations: kg – kilogram; mg – milligram.
Source: Proportion of patients, Clarity AD[135]

A scenario is explored in which wastage is excluded, to determine the impact of vial-sharing. In this scenario, the minimum cost per mg is multiplied by the mean patient weight. Results are presented in Section B.3.11.3.

As detailed in Section B.3.2.4.1, lecanemab is anticipated to be used in addition to SoC. As such, symptomatic treatment costs described in Table 52 and Table 53, are also included for lecanemab.

B.3.5.2.1.1 Administration

Lecanemab is administered via an IV infusion over approximately one hour. There is currently no specific NHS reference cost for the IV infusion of a DMT for AD. Therefore, clinical expert opinion was sought in a UK HTA advisory board (July 2023) to establish the most appropriate proxy.[61] The administration cost for lecanemab was therefore assumed to be £207.59 per infusion, based on the

average cost of a simple parenteral chemotherapy infusion as reported in the NHS reference costs 2021/22 (Table 50).[286] It is possible that once a DMT for AD is established in clinical practice, optimisation of IV therapy delivery may lead to lower administration costs.

Table 50: Lecanemab drug administration cost

Administration cost	Doses per month	Cost per month	Source
£207.59	2.17	£451.32	National Schedule of NHS Costs 2021/22 (SB12Z Simple parenteral chemotherapy at first attendance).[286]

Abbreviations: NHS – National Health Service.

B.3.5.2.1.2 Monitoring

Treatment with lecanemab requires MRI monitoring due to the risk of ARIA. The draft SmPC states [redacted]

UK clinical expert input was sought at a UK HTA Advisory board (July 2023) to inform the frequency of MRI monitoring required in the first year of treatment and beyond.[61] The average of the responses from the four experts indicated that 3.88 MRIs are needed in year 1 and 1.13 are needed in year 2 and beyond which was higher than that stated in the SmPC, therefore was conservatively used in the analysis. The unit cost of an MRI was sourced from NHS reference costs (Table 51).

Table 51: MRI frequency and cost

Year	MRIs per year	Unit cost	Source
1	3.88	£188.11	Frequency: clinical opinion[61] Cost: NHS, National reference Cost Collection 21/22 (RD01A Magnetic resonance imaging scan of one area, without contrast, 19 years and over)[286]
2	1.13		
3	1.13		
4+	1.13		

Abbreviations: MRI – magnetic resonance imaging; NHS – National Health Service.

B.3.5.2.2 Symptomatic treatment costs

Established clinical management includes symptomatic treatments (as outlined in Section B.3.2.4.2). The specific symptomatic treatments approved for AD are AChEIs (donepezil, rivastigmine, and galantamine) and memantine, consistent with NICE guideline NG97.[246]

The proportion of patients receiving symptomatic treatments differs by health state and is informed by Clarity AD, estimated as the proportion of time for which symptomatic treatment was received out of the total time spent by patients whilst in each health state (Table 52). In Clarity AD, use of memantine (which is recommended in the UK for patients with severe AD or patients with moderate AD who are unable to take AChEIs) was observed for patients with MCI due to AD and mild AD. In addition, use of AChEIs was observed for patients with MCI due to AD, for which no pharmacological treatments are recommended in the UK (Section B.1.3.6.2). Irrespective, these proportions were included in the analysis to reflect potential off-label use in UK clinical practice (Section B.2.12.2.1).

Table 52: Symptomatic treatment distribution

Symptomatic treatment	Proportion
AChEI, MCI due to AD	[redacted]
AChEI, mild AD	[redacted]
AChEI, moderate AD	[redacted]
AChEI, severe AD	[redacted]
Memantine, MCI due to AD	[redacted]
Memantine, mild AD	[redacted]
Memantine, moderate AD	[redacted]
Memantine, severe AD	[redacted]

Abbreviations: AD – Alzheimer's disease; AchEI – acetylcholinesterase inhibitors; MCI – mild cognitive impairment.
Source: Eisai Data on file[287]

The cost of AChEIs was calculated using the proportion of patients receiving AChEIs that received donepezil, rivastigmine, or galantamine, respectively, in Clarity AD (Table 53).

Table 53: Symptomatic drug acquisition costs

	Unit cost	% use in Clarity AD	Dose mg/day	Pack size	Source
Cholinesterase inhibitors					
Donepezil	£0.96	77.31	10	10 mg x 28 tablets	eMIT 2022[288]
Rivastigmine	£2.53	14.04	9	4.5 mg x 28 tablets	
Galantamine	£7.70	8.65	16	16 mg x 28 tablets	
Memantine					
Memantine	£0.60	100.0	20	10 mg x 28 tablets	eMIT 2022[288]

Abbreviations: mg – milligram.

All symptomatic treatments considered in the model are administered orally, therefore no administration costs are applied. The estimated monthly costs are reported in Table 54.

Table 54: Monthly drug acquisition costs for symptomatic treatment

Health state	Cost
MCI due to AD	£1.19
Mild AD	£1.60
Moderate AD	£1.82
Severe AD	£2.11

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

B.3.5.3 Diagnostic costs

Treatment with lecanemab is conditional upon confirmation of Aβ pathology as measured by amyloid PET or CSF testing, as per the draft SmPC (Appendix C). As such, the costs of diagnostic testing are included in the base case analysis for patients treated with lecanemab. As per the final scope, a scenario is presented which excludes these costs.

Clinical opinion was sought in the UK HTA advisory board (July 2023) to determine the proportion of patients who would be diagnosed through CSF testing or by PET scan in UK clinical practice. The consensus was that 90% of diagnoses would be via CSF testing, due to PET capacity constraints and scalability of CSF testing. These proportions were applied to the unit costs to calculate the mean diagnostic cost per patient (Table 55).

Table 55: Unit cost for diagnosis and testing

Procedure	Usage	Unit cost	Source
CSF	90%	£295.80	NHS reference costs 2021/22 (Outpatient procedure diagnostic spinal puncture, 19 years and over, neurology service, HC72A)[286]
PET scan	10%	£396.94	NHS reference costs 2021/22 (Weighted cost of Positron Emission Tomography with Computed Tomography [PET-CT] of One Area, 19 years and over [RN01A] and Positron Emission Tomography [PET], 19 years and over, [RN07A])[286]
Expected cost		**£305.91**	Weighted costs of CSF and PET scan

Abbreviations: CSF – cerebrospinal fluid; NHS – National Health Service; PET – positron emission tomography.

Other diagnostic procedures for patients with AD, such as cognitive battery tests, were not included in this analysis as it was assumed these would be used irrespective of treatment hence will not contribute to incremental costs.

B.3.5.4 Health state unit costs and resource use

Health state costs included in the base case analysis are:

- Direct medical costs: healthcare costs, such as primary, community and secondary care services

- Direct non-medical costs: social care costs, such as residential care costs and home-based community care.

As detailed in Section B.3.5 and Appendix I, the SLR identified seven studies reporting the impact of disease severity on cost and/or HCRU, all of which found that cost and HCRU increased as disease severity increased. Only one of these studies (Paquete et al.) reported costs across all disease severities and for both the community and institutional care settings, however costs for MCI due to AD were derived from mild AD costs using the ratio of mild AD to MCI costs reported in a US study (Section B.3.5). As also described in Section B.3.5, the health state costs reported in Paquete et al. were sourced from a report by Alzheimer's Society published in 2014. This report was not identified in the original SLR as it is not a peer-reviewed journal article nor a conference abstract, therefore did not meet the PICOS criteria for publication type.

In light of this, an additional hand search was conducted to identify additional sources of health state costs for the model. The hand search identified one additional relevant study reporting direct medical costs and non-direct medical costs classified according to disease severity (including mild, moderate and severe dementia) and care setting for UK patients; Gustavsson et al. 2011.[289] Both Gustavsson et al. and the Alzheimer's Society report described in Section B.3.5 classified disease severity according to MMSE. No studies were identified reporting results for all model health states including MCI due to AD.[283,289]

Gustavsson et al. evaluated 1,212 patients from Sweden, Spain, the UK (393 UK patients) and the US, and reported costing data separately for each country.[289] A key limitation of this study was that there were a lack of data for patients with mild dementia due to AD in institutions.

The Alzheimer's Society report provides a larger dataset than Gustavsson et al., including data from 59 studies in Western European patients for patients with mild, moderate and severe AD in the community and institutional care settings.[283] When deriving health state costs, data were aggregated from several robust UK trials including START (Livingston 2004, Knapp 2013), SADD (Banerjee 2011, Romeo 2013) and DADE (Lacey 2012, Trigg 2015).[122,290,291] The START trial evaluated strategies for relatives of people with dementia, SADD evaluated the use of antidepressants for depression in dementia (mirtazapine and sertraline) and DADE evaluated the association between dependence and clinical measures of severity.[122,290,291] A previous version of this report was used to inform the model developed by the Assessment Group in TA217.[235] Given that the Alzheimer's Society report provides the largest sample of UK-specific cost data for all model health states, these data were used in the base case analysis, inflated to 2022/23 costs using PSSRU inflation indices (Table 67).[285,292]

Due to the absence of data reported for patients with MCI due to AD, costs for this health state were estimated by applying the ratio of care costs between MCI due to

AD and mild dementia due to AD reported by Robinson et al. (direct medical care costs: 85%) to the mild AD costs from the Alzheimer's Society 2014 report.[109,283] This is consistent with the approach taken by Paquete et al. (Section B.3.5).

B.3.5.4.1 Direct medical costs

Annual direct medical costs for each health state are presented in Table 56. As costs for MCI were not reported in any of the studies identified in the SLR, the cost for MCI due to AD was calculated as 85% of the cost for mild AD, as per the ratio of health state US costs reported by Robinson et al. ($4,243 for mild AD and $2,816 for MCI).[109] The annual costs are adjusted to monthly values to align with the model cycle length.

Table 56: Annual direct medical care costs

Health state	Community	Institution
MCI due to AD*	£2,675.07	£4,379.69
Mild AD	£3,147.14	£5,152.58
Moderate AD	£3,083.08	£10,797.07
Severe AD	£12,879.15	£9,940.22

Abbreviations: AD – Alzheimer's disease; MCI – mild cognitive impairment.
Source: Alzheimer's Society 2014[283]

B.3.5.4.2 Direct non-medical costs

Annual direct non-medical costs for each health state are presented in Table 57.[292] Costs for MCI due to AD in the community were estimated using the same method as described for direct medical care costs, using the ratio of direct non-medical costs for MCI and mild AD health state costs reported in Robinson et al. (MCI: $2816; mild AD: $4243).[109] As direct non-medical costs in the institutional care setting are similar across AD disease states, costs in the MCI due to AD health state were assumed equal to the mild AD state. The annual costs were converted to monthly costs to align with the model cycle length.

Table 57: Direct non-medical care costs

Health state	Community	Institution
MCI due to AD*	£1,949.42	£28,613.11
Mild AD	£3,610.04	£28,613.11
Moderate AD	£8,989.82	£29,744.36
Severe AD	£11,938.23	£29,928.27

Abbreviations: AD – Alzheimer's disease; MCI – mild cognitive impairment.
Source: Alzheimer's Society 2014[283]

B.3.5.5 Adverse reaction unit costs and resource use

As described in Section B.3.3.6, ARIA-E, ARIA-H, and infusion-related reactions were the only AEs that met the criteria for inclusion in the cost-effectiveness analysis. In absence of published UK guidelines for the management of these

events, the associated resource use and costs were adapted from lecanemab appropriate use recommendations in the US reported by Cummings et al.[155] This was supplemented with opinion from UK clinical experts with experience in managing these events in the clinical trial setting (Table 58).

Table 58: AE management

Event	Severity	Management
Infusion-related reaction	Mild (Grade 1)	• None
	Moderate (Grade 2)	• Diphenhydramine 25-50mg, repeated every 4-6 hours until symptoms fully resolve. • Paracetamol 500-1000mg, repeated every 6 hours until symptoms fully resolve. • Expected to resolve <24 hours – but in practice likely to be approximately 2-4 hours only.
	Severe-serious (Grade 3+)	• Oral dexamethasone (0.75 mg/day for 2-3 days) or oral methylprednisolone (80 mg twice per day for 2-3 days) • Preventative oral diphenhydramine 25-50 mg and oral paracetamol 650 mg-1,000 mg 30 minutes prior to the next infusion until the patient remains asymptomatic in clinic and at home following 2-4 infusions
ARIA-E and ARIA-H	Mild-moderate	• Clinical assessment • 2 MRI scans
	Severe-serious	• Clinical assessment • 4 MRI scans • Hospitalisation (6 days) • Methylprednisolone 1g IV daily for 5 days • Prednisolone: 80mg for 2 weeks then taper with 50mg (3 days), 40mg (3 days), 30mg (3 days), 20mg (3 days), 10mg (3 days) and stop

Abbreviations: AE – adverse event; ARIA-E – amyloid related imaging abnormality-oedema/effusion; ARIA-H – amyloid related imaging abnormality-microhaemorrhages and haemosiderin deposits

The unit costs of antihistamine (£10.79), paracetamol (£2.56), oral dexamethasone (£2.70), prednisolone (£10.20) and methylprednisolone (£17.30) were obtained from the BNF.[293] The unit costs of a clinical assessment and MRI scan are reported in Section B.3.5.1. It was assumed [redacted] of patients experiencing serious-severe ARIA-E and [redacted] of patients experiencing isolated ARIA-H would require hospitalisation based on Clarity AD.[135] The unit cost of a hospitalisation for ARIA was assumed to be an average of Non-Elective Inpatient - Long Stay: AA23C-G,

Haemorrhagic Cerebrovascular Disorders across CC scores (£5091.95) from the NHS reference costs 2021-22.[286] Total costs per event are reported in Table 59.

AE rates were modelled by severity reported in Clarity AD. The rates of symptomatic and asymptomatic ARIA-H and ARIA-E were modelled as opposed to symptomatic only, to reflect the associated appropriate use recommendations. The rate of infusion-related reactions for standard of care was assumed to be 0% given these patients will not receive a placebo infusion in clinical practice.

Table 59: AE rates and costs per event

Event	Severity*	Lecanemab	SoC	Source	Cost per event
Infusion-related reaction	Mild	[redacted]	[redacted]	Section B.2.10.4.3	£0.00
	Moderate	[redacted]	[redacted]		£0.00
	Severe	[redacted]	[redacted]		£3.26
	Serious	[redacted]	[redacted]		£6.75
ARIA-E	Mild	[redacted]	[redacted]	Section B.2.10.4.1	£418.22
	Moderate	[redacted]	[redacted]		£418.22
	Severe	[redacted]	[redacted]		£4,572.48
	Serious	[redacted]	[redacted]		£4,572.48
ARIA-H	Mild	[redacted]	[redacted]	Section B.2.10.4.2	£418.22
	Moderate	[redacted]	[redacted]		£418.22
	Severe	[redacted]	[redacted]		£5,008.93
	Serious	[redacted]	[redacted]		£5,008.93

*ARIA-E and ARIA-H based on maximum radiographic severity. Infusion-related reactions are based on NCI-CTCAE criteria; mild = grade 1, moderate = grade 2, severe = grade 3, serious = grade

B.3.5.6 Caregiving costs

As per Section 4.4.24 of NICE's methods manual for health technology evaluations, the costs of unpaid care that might otherwise have been provided by the NHS or PSS may be considered as part of an NHS and PSS perspective.[228] Given unpaid care accounts for 40% of the total costs of dementia care in the UK (Section B.3.2.2), costs borne by unpaid caregivers were included as a scenario analysis.

Unpaid caregiving includes both active caring activities (i.e., assisting with daily activities) and indirect activities (e.g., cooking and cleaning). The costs of unpaid care are taken from the Alzheimer's Society 2014 study and inflated to 2022 prices using the PSSRU inflation indices, as per direct medical and non-medical costs (Section B.3.5.3) (Table 60).[283,294] The study includes replacement cost methods (the

cost of an hour of unpaid care equal to the cost of employing a professional carer such as a home care worker) and opportunity cost methods (this method attempts to reflect the value to carers of the activities that they are no longer able to carry out because of their caring commitment) to estimate unpaid caregiving costs. Hands-on care (such as time spent performing household tasks [e.g., cooking]) was valued using replacement cost methods while other caregiving hours were valued at opportunity cost. The costs of caring for a patient with MCI due to AD is calculated as 45% of the costs of caring for patient with mild AD, as per Robinson et al. (see Section B.3.5.4).[109]

Table 60: Unpaid care costs

Health state	Community	Institution
MCI due to AD	£10,261.37	£555.39
Mild AD	£22,803.04	£1,234.19
Moderate AD	£37,288.31	£3,355.57
Severe AD	£38,728.39	£2,451.03

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

B.3.6 Severity

Despite the chronic nature of AD, it being the leading cause of death in the UK in 2022 (11.4% of all deaths),[295] and its substantial burden (Section B.1.3.4.1), lecanemab does not meet the criteria for a severity weight based on the absolute and proportional QALY shortfall methodology specified in the NICE manual (Table 63). Table 61: details the factors used for the QALY shortfall analysis, while Table 62 details the health state utility values and associated undiscounted life years spent in each health state for AD patients receiving SoC.

The absolute QALY shortfall for considering a QALY modifier (≥12 QALYs) is not achievable for this early AD population due to the average age (71 years in Clarity AD), which yields expected total QALYs for the general population of 8.78. This reflects how absolute shortfall biases against older populations given that potential life-years are constrained by life expectancy.[296]

Moreover, the estimated proportional QALY shortfall (48%) for this early AD population is substantially below the 85% threshold for a QALY modifier due to the chronic nature of early AD. This reflects how proportional shortfall, while seeking to address potential age-bias induced in absolute shortfall, arguably biases against chronic conditions such as early AD.

Table 61:Summary features of QALY shortfall analysis

Factor	Value	Reference to section in submission
Sex distribution	52.3% female	B.3.2.1
Starting age	71.2 years	B.3.2.1
Discount rate	3.5%	B.3.2.2

Remaining LY of population	UK life tables	Life tables England 2017-2019 (pooled)[297]
Remaining QALY of population	UK population utility norms	• Scoring algorithm: EQ-5D-3L value set from the 1993 MVH study[298] • Health state profiles: EQ-5D-3L from the Health Survey for England 2014[299] • Model: ALDVMM by Hernandez Alava, et al. 2022[300]
Health state utility values	Values from Clarity AD and Farina et al.	B.3.4.4.1
Caregiver disutilities	Values from Black et al.	B.3.4.4.2

Abbreviations: LY – Life year; QALY – Quality-adjusted life year

Table 62: Summary of health state benefits and utility values for QALY shortfall analysis

State	Utility value: mean (standard error)*	Undiscounted life years
MCI due to AD, community	0.88 (0.13)	[redacted]
Mild, community	0.87 (0.13)	[redacted]
Moderate, community	0.67 (0.3**)	[redacted]
Severe, community	0.57 (0.3**)	[redacted]
MCI due to AD, institution (disutility)	-0.01 (-0.06)	[redacted]
Mild, institution (disutility)	-0.01 (-0.06)	[redacted]
Moderate, institution (disutility)	-0.16 (-0.06)	[redacted]
Severe, institution (disutility)	-0.16 (-0.06)	[redacted]

Abbreviations: AD – Alzheimer's disease; MCI – mild cognitive impairment; LY – Life year; QALY – Quality-adjusted life year

*Not inclusive of carer utilities. **Utility values for moderate and severe AD community health states are calculated through a decrement applied to the mild AD community health state, therefore SEs reported for moderate and severe AD are that of the original utility values.

Table 63: Summary of 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	Proportional QALY shortfall
8.78	4.58	4.20	47.83%

Abbreviations: QALY – quality-adjusted life year

B.3.7 Uncertainty

The ability to generate high-quality evidence for this appraisal is influenced by the chronic nature of AD, in combination with the target population for lecanemab being early AD, and the absence of a regulatory approved disease-modifying therapy for early AD.

The chronic nature of AD means it can take many years for early AD patients to progress through the various stages of disease severity (Section B.1.3.2), with patients typically living for four to eight years following diagnosis, reaching 20 years in some cases.[58] Consequently, key outcomes for the economic analysis, such as progression to more severe disease states, institutionalisation, and death, occur beyond the timeframe of a clinical trial such as Clarity AD for most patients. Moreover, data for patients with MCI due to AD are sparse, given this is a recently emerging patient population and there are no existing pharmacological interventions for this population. AD patients with Aβ pathology are expected to progress at a higher rate than those without, however associated data for this population are also sparse, as amyloid confirmation is not routine for current AD diagnoses.

From the perspective of economic modelling and the need to estimate clinical outcomes over a lifetime horizon, this presents a challenge likely to induce uncertainty due to the length of follow-up required to generate these data in clinical trials. This uncertainty has been minimised in the economic analysis by using published natural history data for patients with confirmed amyloid pathology identified via a SLR, however these data are not UK-specific. While data from a UK population would be preferable, no sources were identified as part of the SLR or additional hand searches. Any remaining uncertainty for SoC disease progression is unavoidable due to the sample size and follow-up required.

Patient-reported HRQoL data such as EQ-5D and the associated utility values, are only suitable for less severe health states due to the substantial divergence between patient reported and proxy caregiver reported EQ-5D scores observed with increasing AD severity, with patients typically rating their own HRQoL considerably higher than ratings given by their caregivers (Section B.3.4.4.1). Therefore, it is hard to understand the true HRQoL of AD patients while adhering to the NICE reference case.

In the absence of a regulatory approved disease-modifying therapy for early AD combined with the chronic nature of the disease, long term data for this new class of therapy are very limited. While the 18-month duration of the Clarity AD core study is consistent with other RCTs in this patient population, and lecanemab has demonstrated a statistically significant and clinically meaningful effect on established, validated, globally accepted endpoints during this follow-up, this interval represents a fraction of the time over which the underlying AD pathophysiology has evolved. Therefore, in contrast to symptomatic treatments currently used to manage AD, it is possible that the cumulative benefit of lecanemab may not be apparent to patients and family members until years after the intervention.[159] This is particularly relevant given lecanemab is expected to be administered beyond the 18 months Clarity AD core study follow-up in clinical practice, subject to regulatory approval. Given it is not practical to conduct RCTs over one or two decades, uncertainty surrounding the cumulative long-term benefit of lecanemab on endpoints used in the economic analysis such as disease progression and HRQoL is unavoidable at this

stage.[159] This extends to the impact on caregivers despite the extensive data collected in Clarity AD.

Consequently, the economic analysis relies on assumptions and clinical expert opinion, as is common in HTA. Clinical input was sought via a UK HTA advisory board conducted in July 2023 and subsequent follow-up questions (Section B.3.14). Further data collection is ongoing via the Clarity AD OLE study, however this will not resolve the uncertainties described within the timeframe of this appraisal.

Uncertainty in the model parameters was explored through one-way sensitivity analysis (OWSA) and probabilistic sensitivity analysis (PSA). Extensive scenario analyses were also conducted to assess the impact of alternative assumptions and data sources which were not captured within the OWSA and PSA (Section B.3.11).

B.3.8 Managed access proposal

It is widely acknowledged that lecanemab has the potential to address the substantial unmet need in AD (Section B.1.3.7) and provide clinically significant benefits to early AD patients and caregivers, subject to MHRA approval.[193,195]

B.3.9 Summary of base-case analysis inputs and assumptions

B.3.9.1 Summary of base-case analysis inputs

A summary of the variables applied in the economic model is provided in Table 64.

Table 64: Summary of base-case variables applied in the economic model

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: confidence interval (distribution)	Reference to section in submission
Natural history transitions	Table 40 Table 41	Beta (arbitrary SE=20% of the mean)	B.3.3.1
Institutionalisation	Table 42	Mild AD: Beta (SE=0.00) Moderate AD, Severe AD: Beta (SE=0.01)	**Error! Reference source not found.**

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: confidence interval (distribution)	Reference to section in submission
Treatment effectiveness	B.3.3.1.3	Beta (arbitrary SE=20% of the mean)	
Mortality	Table 43	MCI: Gamma (SE=0.11) Mild AD: Gamma (SE=0.37) Moderate AD: Gamma (SE=0.68), Severe AD: Gamma (SE=2.00)	B.3.3.5
Treatment discontinuation	17.9%	Beta (arbitrary SE=20% of the mean)	B.3.3.2
Adverse event frequencies	Table 44	IRR events: Beta (SE=95% CI) ARIA-E and ARIA-H: Beta (SE=95% CI)	B.3.3.6
Patient utilities	Table 45	MCI, Mild AD: Beta (arbitrary SE=20% of the mean) Moderate AD: Beta (SE=0.12) Severe AD: Beta (SE=0.09)	B.3.4.4.1
Caregiver utilities	Table 46	Community: MCI, Mild AD, Moderate AD, Severe AD: Beta (SE=95% CI) Institution: MCI, Mild AD, Moderate AD, Severe AD: Beta (SE=95% CI)	B.3.4.4.2
Symptomatic treatment distribution	Table 52	Beta (arbitrary SE=20% of the mean)	B.3.5.2.2
Direct medical care costs	Table 56	Gamma (arbitrary SE=20% of the mean)	B.3.5.4.1
Direct non-medical care costs	Table	Gamma (arbitrary SE=20% of the mean)	B.3.5.4.2

Abbreviations: AD – Alzheimer's disease; MCI – mild cognitive impairment; SE – Standard error

B.3.9.2 Assumptions

A summary of the key assumptions in the base case model is provided in Table 65.

Table 65: Summary of key model assumptions

Aspect	Assumption	Justification
Model structure	A Markov model structure is appropriate for early AD.	Markov models were used in over half of the UK studies identified in the SLR. In TA217, the committee showed a preference for the Markov modelling approach over a DES as the latter required more data inputs which could not be adequately populated from the UK-specific literature.
Health states	Four disease severity stages including MCI due to AD, mild AD, moderate AD and severe AD are based on location of care (either community or institution); this generates 8 of the model health states.	The model captures the progressive nature of AD, the increased risk of institutionalisation as disease severity worsens and the associated cost and HRQoL effects. The health states are defined based on well-established methods of disease classification and are consistent with the broad literature on modelling in AD (see Section B.3.2.3.1).
Half-cycle correction	Costs and QALYs are modelled based on midpoint estimates assuming that patients, on average, transition mid-way through the model cycle.	This is a standard approach to mitigate the risk of under or over-estimating costs and effects.
Cycle length	One month.	To reflect bi-weekly lecanemab infusions, to ensure the complex resource use and associated costs for patients with AD were comprehensively captured, and to reduce bias associated with long cycle lengths.
Mortality	Mortality is based on hazard ratios vs. cognitively normal individuals reported in Crowell et al. and mortality increases as disease severity worsens.	The natural history SLR did not identify mortality estimates defined using CDR-SB. A hand search identified Crowell et al. which reported hazard ratios across all stages from the Uniform Data Set of the NACC database.[268]
Natural history	AD natural history progression beyond 18-months is modelled using transition probabilities derived from Potashman et al.	This approach is consistent across the AD modelling literature reviewed as part of this appraisal.
Institutionalisation	Risk of institutionalisation increases with disease severity. Once a patient is institutionalised, they cannot transition back to a community setting.	This is consistent with the available literature.[61,204,239,256]
Stopping rules	Discontinuation upon progression to moderate AD.	[redacted] This aligns with clinical feedback at a UK HTA advisory board (July 2023) that the overriding principal for stopping treatment should be to prolong patients time in earlier stages of disease, where they remain independent and have better QoL.
	Discontinuation upon entering institutional care.	Consensus was reached among clinical experts at a UK HTA advisory board (July 2023) that patients would not be treated with a DMT in an institution.[61]

Durability of effect	[redacted]	[redacted]
Utilities	Patient-reported utility values are used for MCI and mild AD health states, whilst patient-by-proxy utility values are used for moderate and severe AD health states.	It has been observed that patient-reported and patient-by-proxy reported EQ-5D scores diverge substantially as AD severity increases. This divergence was noted by PenTAG for TA217, who noted that patients self-report much higher utility values compared to those estimated by their carers.[243] Clinical feedback from a July 2023 UK advisory board indicated that it is appropriate to switch from patient-reported utilities to patient-by-proxy reported utilities for patients in later stages of AD, specifically at moderate AD.[61]
Inclusion of caregiver disutility	Caregiver HRQoL is considered in the analysis.	Most patients with AD require assistance from an unpaid carer to support their day-to-day activities.[276] Approximately 95% of carers have reported a negative impact on their mental or physical health.[278] Therefore, caregiver utilities are included in the economic analysis to capture the associated burden of AD.
Use of utility decrement method for caregiver HRQoL	Caregiver HRQoL is modelled through the utility decrements relative to the MCI health applied to more severe health states.	The most appropriate method to apply caregiver utility in cost-effectiveness analysis is not well defined, and a preferred approach is not specified in the NICE health technology evaluation manual.[200] In a review of the application of carer HRQoL in NICE appraisals, Pennington et al. found that 11 of 16 appraisals used utility decrements for carers, modelled as a function of the patient's health state.[279]
Administration costs	Cost of lecanemab administration assumed to be the same as delivery of simple parenteral chemotherapy at first attendance (NHS reference cost code SB12Z).	There is currently no specific NHS reference cost for the IV infusion of a DMT in AD, therefore a proxy administration cost was required. Clinicians at a July 2023 UK advisory board advised that the cost of administration for patients receiving lecanemab would be constant over time, and that the cost of administering chemotherapy could be representative of the incurred costs.[61]

Abbreviations: AD – Alzheimer's disease; MCI – mild cognitive impairment; QALY – Quality=adjusted life year; UK – United Kingdom

B.3.10 Base-case results

B.3.10.1 Base-case incremental cost-effectiveness analysis results

B.3.10.1.1 Incremental benefits

The economic analysis estimates a slower rate of disease progression for lecanemab compared with SoC, as observed in Clarity AD. Specifically, treatment with lecanemab delays onset of moderate AD by [redacted] years. Consequently, patients treated with lecanemab spend more time in early AD ([redacted] incremental LYs) and less time in moderate and severe AD ([redacted] incremental LYs), compared to patients treated with SoC alone. The estimated mean time on treatment with lecanemab is [redacted] years based on the stopping rules described in Section B.3.3.3.

Lecanemab also indirectly reduces the risk of institutionalisation through slowing of disease progression to more severe health states in which risk is higher. Lecanemab therefore increases the time patients spend in community care ([redacted] incremental LYs) (Table 57 in Appendix J1.2) and reduces time spent in institutional care compared with SoC ([redacted] vs. [redacted] years, respectively).

Overall, these benefits of lecanemab translate to a survival benefit of [redacted] years due to the delayed time to more severe stages of AD with associated increased mortality. Similarly, lecanemab generates an increase in discounted QALYs of [redacted] versus SoC (Table 66 and Appendix J) due to the relatively greater time spent in early AD in community care, which has multiple HRQoL benefits for patients and their caregivers.

B.3.10.1.2 Incremental costs

Costs associated with lecanemab (including acquisition, administration, diagnostic testing, monitoring, and management of AEs) were partially offset by reductions in direct medical costs (-[redacted]) and direct non-medical care costs (-£[redacted]) versus SoC. The primary drivers of the incremental costs ([redacted]) associated with lecanemab are the acquisition and administration costs (Table 66 and Appendix J)given the extremely low cost of orally-administered SoC symptomatic treatments.

B.3.10.1.3 Incremental cost-effectiveness

[redacted]

Based on the list price for lecanemab, the cost-effectiveness of lecanemab compared with SoC is £[redacted] per QALY gained (Table 66). Lecanemab generates an additional [redacted] QALYs at an additional cost of £[redacted].

Table 66: Base-case results

Technologies	Total			Incremental			ICER (per QALY)	NHB at £30,000
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs		
SoC	[redacted]	[redacted]	4.58	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lecanemab	[redacted]	[redacted]	[redacted]	[redacted]				

Abbreviations: ICER – Incremental cost-effectiveness ratio; LYG – life years gained; NHB – net health benefit; QALY – quality-adjusted life year; SoC – standard of care

B.3.11 Exploring uncertainty

B.3.11.1 Probabilistic sensitivity analysis

Joint parameter uncertainty was explored through PSA, in which all appropriate parameters are assigned distributions and varied jointly. Those not appropriate for variation include structural assumptions (e.g., cell links for model options, time horizon) and those considered to be certain (e.g., drug acquisition costs). A total of 10,000 Monte Carlo simulations were recorded and plotted over time to demonstrate ICER convergence. Results were plotted on the incremental cost-effectiveness plane (Figure 35) and a cost-effectiveness acceptability curve (CEAC) (Figure 36) was generated presenting the percentage of simulations in which lecanemab is cost-effective over willingness-to-pay (WTP) thresholds from £0-100,000 per QALY gained.

The mean costs and QALYs were comparable to the base case values, resulting in a probabilistic ICER just £[redacted] lower than the base case ICER (£[redacted], Table 67).

Table 67: PSA base-case results

Technology	Total		Incremental		
	Costs (£)	QALYs	Costs (£)	QALYs	ICER (per QALY)
SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lecanemab	[redacted]	[redacted]			

Abbreviations: ICER – incremental cost-effectiveness ratio; LYG – life years gained; NHB – net health benefit; PSA – probabilistic sensitivity analysis; QALY – quality-adjusted life year; SoC – standard-of care

Figure 35: Incremental cost-effectiveness plane

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

Figure 36: Cost-effectiveness acceptability curve

Abbreviations: SoC - standard of care

B.3.11.2 One-way sensitivity analysis

One-way sensitivity analysis (OWSA) was conducted by varying one parameter at a time and assessing the subsequent impact on cost-effectiveness. By adjusting each parameter individually, the sensitivity of the model results to that parameter can be assessed.

The OWSA was conducted by allocating a 'low' value and a 'high' value to each parameter; the low value is the lower bound of the 95% CI, the high value is the upper bound of the 95% CI**.** In the absence of CI data, the variable was altered by +/-

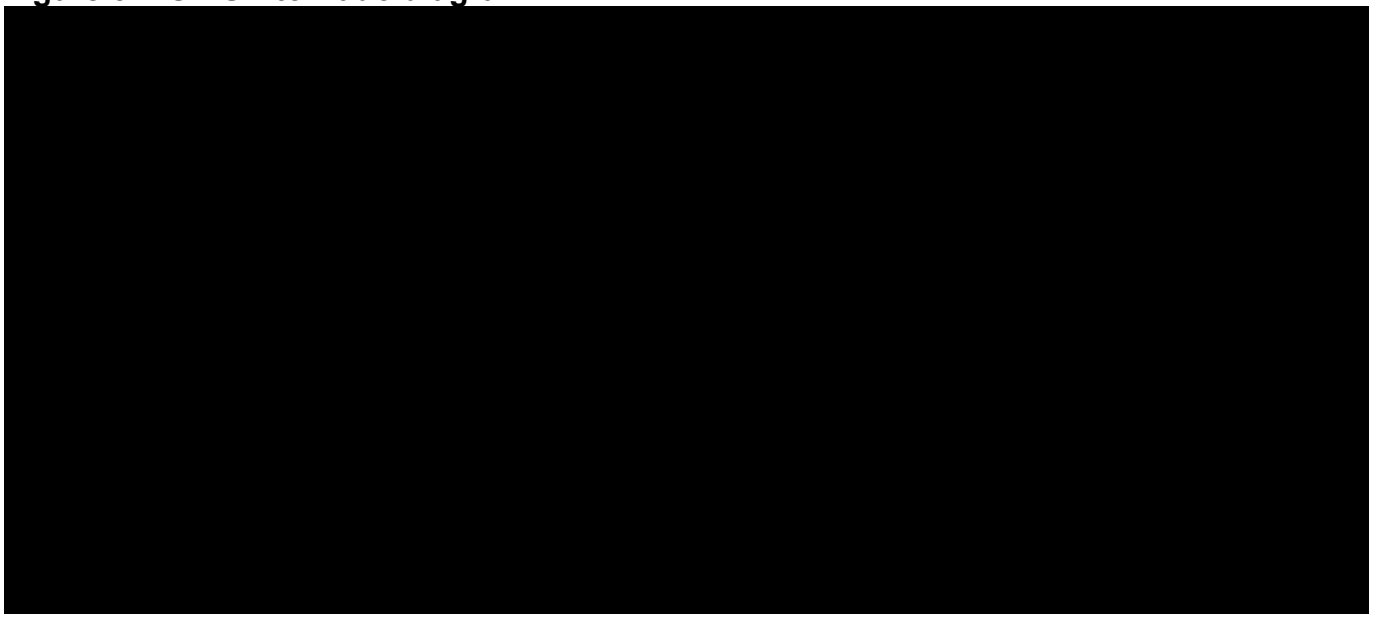
20%. A OWSA tornado diagram presenting the top ten most sensitive parameters is presented with tabulated results presented in Table 68. The parameters yielding the biggest impact on cost-effectiveness results are time to worsening HRs for mild AD and MCI due to AD, and the Farina patient-by-proxy health state utility values for mild, moderate, and severe AD. The SEs reported by Farina et al. were very large relative to the means (0.3 for all health states compared with means of 0.7, 0.5, and 0.4, respectively). Therefore the variation in results is likely attributable to uncertainty in the Farina et al. study, rather than the health state utility values being key drivers of results.

Table 68: Tabulated OWSA results for lecanemab vs SoC

Parameter	Lower bound ICER (£)	Upper bound ICER (£)	Difference (£)
Time to worsening HR, mild AD (CDR-SB)	[redacted]	[redacted]	[redacted]
Time to worsening HR, MCI due to AD (CDR-SB)	[redacted]	[redacted]	[redacted]
Utility: Farina (carer as proxy) - Mild AD	[redacted]	[redacted]	[redacted]
Utility: Farina (carer as proxy) - Severe AD	[redacted]	[redacted]	[redacted]
Lecanemab compliance	[redacted]	[redacted]	[redacted]
Utility: Farina (carer as proxy) - Moderate AD	[redacted]	[redacted]	[redacted]
Discontinuation rate: Clarity, all cause - lecanemab	[redacted]	[redacted]	[redacted]
Potashman, MCI due to AD to AD	[redacted]	[redacted]	[redacted]
Mortality rate: Crowell - MCI due to AD	[redacted]	[redacted]	[redacted]
Lecanemab cost of administration	[redacted]	[redacted]	[redacted]

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

Figure 37: OWSA tornado diagram



Abbreviations: AD - Alzheimer's disease; CDR-SB – Clinical dementia rating – sum of boxes; HR – hazard ratio; ICER – incremental cost-effectiveness ratio; MCI – mild cognitive impairment.

B.3.11.3 Scenario analysis

Extensive scenario analyses were performed to test underlying model assumptions and the use of alternative input parameters. The list of scenarios explored is presented in Table 69.

The results are generally stable and the ICER improves in most scenarios versus the base case (Table 70), indicating that the base case settings are likely to be conservative. Of note is the scenario in which CDR global rather than CDR-SB is used to define health states, transitions in the first 18-months, and the lecanemab treatment effect beyond 18-months. In this scenario, the ICER reduces by [redacted] per QALY gained. CDR-SB is used in the base case to align with the primary endpoint of Clarity AD, and due to the absence of CDR global natural history data. However, CDR global was cited in a UK HTA Advisory Board (July 2023) as a preferable measure of AD progression.[61] Assuming that the natural history transition probabilities from Potashman et al. 2021 are an appropriate proxy for CDR global risk, this indicates that the true benefit of lecanemab is underestimated in the base case, thus the cost-effectiveness of lecanemab is likely more favourable than is presented in the base case.[251] Further of note is the scenario exploring [redacted]. In this scenario, the ICER is reduced to £[redacted].

The results and interpretation of the scenario analyses are further discussed in Section B.3.15.

Table 69: Scenarios explored in the cost-effectiveness analysis

#	Category	Base case	Scenario	
		Value	Value	Rationale
1, 2	Annual discount rate for costs and QALYs	3.5% for costs and outcomes	(1) 1.5% for costs and outcomes (2) 3.5% for costs, 1.5% for outcomes	(1) As per NICE guidelines.[301] (2) A 1.5% discount for outcomes alone is an important consideration in the context of this appraisal, where health benefits are accrued in later years through delayed disease progression.
3, 4	Baseline age (years)	71.2 (Clarity AD mean baseline age)	(3) 60 (4) 65	(3, 4) The vast majority (97%) of patients diagnosed with dementia are over the age of 65 (Section B.1.3.3).[77] However, with increased NHS emphasis on diagnosing dementia early, it is reasonable that the mean baseline age of patients starting AD therapy will decrease over time.[302]
5	Health state definition	CDR-SB	Global CDR	Global CDR was identified as a useful measure of AD progression by clinical experts at the UK HTA advisory board (July 2023) (Section B.3.2.3.1).[61]
6	Diagnostic testing costs	Included	Excluded	As per the final scope.[2]
7	Wastage	Applied	Not applied	To consider the availability of vial-sharing.
8	Switch to natural history data (year)	1.5	0	(9) To determine the impact on clinical and cost-effectiveness outcomes when natural history data is used from baseline; in this analysis, the treatment effect of lecanemab from Clarity AD is used, but the transition probabilities from Clarity AD for either arm are not used.
9	Lecanemab treatment effect	[redacted]	[redacted]	[redacted]
10	Institutionalisation source	Knapp et al.	Belger et al.	Alternative UK-specific source of institutionalisation risk.
11	Mortality	Crowell	Crowell with HR=1 for MCI	The HR for mortality in the MCI due to AD health state reported by Crowell is below 1, thus this is a conservative scenario assuming an

#	Category	Base case	Scenario	
		Value	Value	Rationale
				equal mortality rate to that of the cognitively normal population within the MCI health state.
12	Patient health state costs	Direct medical and non-medical costs for MCI approximated from Alz Soc report and Robinson	Exclude direct medical and non-medical care costs in MCI	Health state costs are sourced from an Alzheimer's Society report, however this report did not include costs for MCI due to AD. As such, costs for this health state were estimated by applying the ratio of care costs between MCI due to AD and mild dementia due to AD reported by Robinson et al, a US-based study.[109,292] Due to the paucity of UK-specific data on health state costs for MCI due to AD, this analysis considers only the costs as reported by the Alzheimer's Society, for mild, moderate, and severe AD.
13, 14	Unpaid care costs	Excluded	(13) Included (14) Included for mild moderate and severe AD but excluded for MCI	(13) To align with NICE's methods manual for health technology evaluations, the cost of providing unpaid care (by family members, friends, or a partner) which might otherwise have been provided by the NHS or PSS, can be considered within the NHS and PSS perspective (Section B.3.2.2).[5] (14) As per scenarios 12 and 13.
15	Monitoring costs	3.875 MRIs assumed in year one	3 MRIs in year one	The draft SmPC for lecanemab states [redacted] The frequency of MRIs in year 1 in the base case was conservatively assumed to be 3.88, aligning with UK clinical expert input from a 2023 UK HTA Advisory board.[61] To align with the draft SmPC, and in case of double counting with the cost of MRIs for ARIA, this scenario considers 3 MRIs.
16	Source of patient HSUVs in moderate and severe AD	Farina et al.	Landeiro et al.[95]	Landeiro et al. meta-analysed EQ-5D utility estimates from 48 studies identified via a SLR. Whilst these data include ex-UK studies, and therefore weren't considered for the base case, they provide health state utility estimates from a large sample of AD patients.

#	Category	Base case	Scenario	
		Value	Value	Rationale
17	Caregiver (dis)utility approach	Utility decrement	Patient and caregiver additive	The most appropriate method to apply caregiver utility in cost-effectiveness analysis is not well defined. The approach used in the base-case analysis, with decrements relative to the MCI health state being applied in more severe health states, has the undesirable property that if a patient dies, the decrement ceases to be incurred, therefore disadvantaging lecanemab through as this extends the life of patients. This assumption is not consistent with patients' and carers' preferences and raises the issue of how QALYs accruing to patients and carers should be valued where an intervention may lead to gains for one and a loss for the other (Section B.3.4.4.2).[279] As such, in this scenario, caregiver utility is modelled as the absolute QoL for both caregivers and patients summed in each cycle, as reported by Large.[280] This approach includes caregivers as separate entities, with quality of life included using the absolute utility based on the health state that the patient resides.
18, 19	Caregiver utility source for moderate and severe AD	Black	(18) Lopez-Bastida[272] (19) Mesterton[36]	Alternative sources of caregiver health state utilities measured through EQ-5D-3L.
20, 21	Baseline disease severity	Proportions as per Clarity AD	(20) 100% MCI (21) 100% mild AD	(20, 21) As per the final scope (Table 1).[2]
22	Clinical subgroup and baseline age	MCI and mild AD proportions and baseline age as per Clarity AD	100% of patients starting in MCI with a baseline age of 65 years	To reflect diagnosis being achieved earlier in the disease as the NHS adapts to introduction of a DMT, patients are more likely to be diagnosed before reaching moderate AD, at a younger age.

Abbreviations: AD – Alzheimer's disease; ARIA – amyloid-related imaging abnormalities; CDR – Clinical Dementia Rating; CDR-SB – Clinical Dementia Rating Scale - Sum of Boxes; DMT – disease modifying therapy; HR – hazard ratio; HSUV – health state utility value; HTA – health-technology assessment; MCI – mild cognitive impairment; MRI – magnetic resonance imaging; NICE – National Institute for Health and Care Excellence; PSS – Personal social services; QALY – quality-adjusted life year; QoL – quality of life; SLR – systematic literature review; SmPC – Summary of Product Characteristics; UK – United Kingdom

Table 70. Scenario analysis results

#	Scenario	Deterministic ICER	Probabilistic ICER
	Base case	[redacted]	[redacted]
1	1.5% discount for costs and outcomes	[redacted]	[redacted]
2	3.5% discount for costs, 1.5% discount for outcomes	[redacted]	[redacted]
3	Baseline age = 60 years	[redacted]	[redacted]
4	Baseline age = 65 years	[redacted]	[redacted]
5	Health state definition: Global CDR	[redacted]	[redacted]
6	Diagnostic testing costs excluded	[redacted]	[redacted]
7	No wastage	[redacted]	[redacted]
8	Switch to natural history data at baseline (0 years)	[redacted]	[redacted]
9	Assume lifetime lecanemab benefit	[redacted]	[redacted]
10	Source of institutionalisation probabilities: Belger	[redacted]	[redacted]
11	Source of mortality: Crowell with HR=1 for MCI	[redacted]	[redacted]
12	Patient health state costs: Excluded for MCI	[redacted]	[redacted]
13	Unpaid care costs: Included	[redacted]	[redacted]
14	Unpaid care costs: Included for mild moderate and severe AD, excluded for MCI	[redacted]	[redacted]
15	Monitoring costs: 3 MRIs in year 1	[redacted]	[redacted]
16	Source of patient HSUVs in moderate and severe AD: Landeiro	[redacted]	[redacted]
17	Caregiver (dis)utility approach: patient and caregiver additive	[redacted]	[redacted]
18	Caregiver utility source for moderate and severe AD: Lopez-Bastida	[redacted]	[redacted]
19	Caregiver utility source for moderate and severe AD: Mesterton	[redacted]	[redacted]
20	Population at baseline: MCI due to AD only	[redacted]	[redacted]
21	Population at baseline: Mild AD only	[redacted]	[redacted]
22	Population and age at baseline: MCI due to AD, 65 years	[redacted]	[redacted]

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

B.3.12 Subgroup analysis

Formal subgroup analysis has not been conducted, as the statistical analysis of the primary and secondary efficacy endpoints from the Clarity AD trial derived no statistically significant differences in treatment effects by subgroups (Section B.2.7, Appendix E). Scenarios considering the MCI due to AD and mild AD populations separately have been presented in Section B.3.11.3.

B.3.13 Benefits not captured in the QALY calculation

Lecanemab is expected to generate numerous health-related benefits that are unlikely to be captured in the QALY calculation. AD presents a uniquely complex and widespread burden that falls outside of the current framework, through strain on caregivers and families' health, finances, and productivity.[303]

Whilst the impact of AD on caregiver everyday functioning is widely recognised and it is therefore important to consider these HRQoL effects, the commonly used decrement method for capturing caregiver utilities adopted in the base case for consistency with previous HTAs and in absence of a preferred approach stated by NICE can penalise life-extending treatments. By considering decrements to HRQoL only, lecanemab is penalised for keeping patients alive as the associated decrement is applied for the extended survival time ([redacted] undiscounted life years in base case), despite being partly offset by the HRQoL benefit for caregivers in early AD. This challenge is referred to as the 'carer QALY trap' in the published literature by Mott et al.[304]

A scenario is presented in which caregiver utility is modelled as the absolute HRQoL for both caregivers and patients summed in each cycle, to avoid the disadvantage seen with the decrement approach through which a patient dying implies caregiver QoL improves as the decrement ceases to be incurred (Section B.3.4.4.2). The ICER is [redacted]% lower than the base case ICER in this scenario, highlighting the extent of the potential 'true' benefit to caregivers QoL of lecanemab and indicating the conservative nature of the selected base case.

Beyond the method used for modelling caregiver utility, there are additional components of caregiver QoL and wellbeing that are not captured within the QALY calculation. Behavioural changes in the patient, such as aggression, are particularly disturbing for caregivers. Caregivers may develop mental health problems and family relationships may be strained.[305,306] The stages of grief experienced by a caregiver of someone with AD are complex. Many caregivers have described 'losing their loved one twice'; following diagnosis in the face of no curative or effective treatments, caregivers face a feeling of loss for the person they once knew and who knew them in return, amplified by uncertainty as to how much quality time they have

remaining, followed by the eventual grieving of the physical loss of their loved one.[307–309]

The burden on caregivers of patients with AD also extends to their time, productivity, and finances. Unpaid caregiving costs are substantial in AD (Section B.1.3.5.2), but apply only when a patient is alive, thus penalising lecanemab for keeping patients alive for longer and in better states of health. Whilst patients remain in less severe disease states, they are less likely to be institutionalised, thus continuing to incur unpaid caregiving costs. In addition, productivity losses are associated with caregiver absenteeism and health problems such as stress and depression, which are not captured in this analysis[120,277,310].

As discussed in Section B.3.6, it is not possible for treatments for early AD to achieve severity modification via the absolute or proportional shortfall methods, due to the age of the population and the chronic nature of AD. This is despite AD being the leading cause of death in the UK in 2022 and its substantial burden, and consensus in the clinical community that the focus of therapies should be to extend time in milder disease states.[311]

B.3.14 Validation

In line with the International Society for Health Economics and Outcomes Research (ISPOR) taskforce report on model transparency and validation,[312] the following types of validation were conducted:

- Internal validation
- Cross validation
- External validation

The results of validation are presented in the subsequent sections.

B.3.14.1 Internal validity

Internal validation was conducted once by the primary modeller and once by a modeller external to the project, and included:

- Cell-by-cell checks of formulae
- Rebuilding of key sections of the model
- Logical tests
- A full audit of model inputs

Any issues were addressed within the analysis.

B.3.14.2 Cross-validity

Model predictions over the first 18 months were compared to data from each scheduled study visit at 13, 27, 39, 53, 65 and 79 weeks in Clarity AD on the distribution of the cohort across the MCI due to AD, mild, moderate and severe AD and death health states. The data from Clarity AD were compared with the model estimate of health state occupancy in the nearest model cycle (Table 71 and Table 72 for the lecanemab and SoC arm, respectively).

The model accurately predicts the state occupancy observed in Clarity AD for both treatments. The minor differences, particularly in mortality, may be explained by the use of life tables in combination with AD mortality estimates from published literature.

Table 71: Lecanemab, Clarity AD vs CEM

	Health state occupancy (%)				
Time	MCI due to AD	Mild AD	Moderate AD	Severe AD	Death
Clarity-AD					
13 weeks	[redacted]				
27 weeks	[redacted]				
39 weeks	[redacted]				
53 weeks	[redacted]				
65 weeks	[redacted]				
79 weeks	[redacted]				
CEM					
3 months	[redacted]				
6 months	[redacted]				
9 months	[redacted]				
12 months	[redacted]				
15 months	[redacted]				
18 months	[redacted]				

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

Table 72: SoC, Clarity AD vs CEM

	Health state occupancy (%)				
Time	MCI due to AD	Mild AD	Moderate AD	Severe AD	Death
Clarity-AD					
13 weeks	[redacted]				
27 weeks	[redacted]				
39 weeks	[redacted]				
53 weeks	[redacted]				
65 weeks	[redacted]				
79 weeks	[redacted]				
CEM					
3 months	[redacted]				
6 months	[redacted]				
9 months	[redacted]				
12 months	[redacted]				
15 months	[redacted]				
18 months	[redacted]				

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

B.3.14.3 External validity

The external validity of the analysis was assessed by comparing to a range of published AD models. Handels et al. undertook a cross-comparison challenge for AD models and reported outcomes across two benchmark scenarios as part of the International Pharmaco-Economic Collaboration on Alzheimer's Disease (IPECAD) Modelling Workshop.[313]

Twelve models were submitted to the modelling challenge. Of the twelve models, six were state transitions models four were discrete-time microsimulations, and two were DES.[233,234,239,255,256,314–317]

Scenario A assessed 100% of the population starting in MCI due to AD, while Scenario B assessed 100% of the population starting in mild AD. Ten of the submitted models were in the MCI population and four were in the mild AD population. The publications were compared with the SoC arm of the lecanemab model across the four disease states (MCI due to AD, mild AD, moderate AD, and severe AD; note three of the publications modelling an MCI due to AD population included a single dementia health state. Results for the MCI population are presented in Table 73.

All publications in the IPECAD modelling challenge used benchmark settings to improve comparability across the range of models, such as using a starting age of 70. All models used a 10-year time horizon with costs and QALYs discounted at 3.5% and half cycle correction applied. The lecanemab model settings were not changed from the base case settings aside from the starting health state distribution in each scenario, and comparisons are presented against SoC only given none of the models included within the IPECAD modelling challenge considered lecanemab.

Table 73: Comparison to IPECAD MCI due to AD scenario A (SoC arm)

	Duration of state occupancy (years)			
Model	MCI due to AD	Mild AD	Moderate AD	Severe AD
CPEC (201)	3.63	3.23	1.14	0.54
Davis (146),	3.38	2.97	0.99	0.73
MISCAN (207)	3.46	5.99		
BASQDEM (208)	4.46	2.88	0.36	
ADACE (205)	4.61	1.98	0.73	0.18
Herring (204)	3.52	4.24		
FEM (206)	5.54	2.16		
KP (200)	3.71	1.70	0.54	0.72
SveDem (99)	3.68	2.67	2.02	0.38
IPECAD (199)	4.77	0.97	1.50	0.65
This analysis	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AD – Alzheimer's disease; AD ACE – Alzheimer's disease Archimedes condition-event; CPEC – Care Policy and Evaluation Centre; FEM – Future Elderly Model; IPECAD – International Pharmaco-Economic Collaboration on Alzheimer's Disease; MCI – mild cognitive impairment; MISCAN – Microsimulation Screening Analysis; SoC – standard of care.

This analysis predicts state distributions aligned with those observed in the IPECAD modelling challenge. All models, with the exception of those which merged AD health states, predict MCI due to AD to have the longest state occupancy of all health states. The duration of MCI state occupancy is broadly similar across all models. Mild AD is commonly the health state with the second longest duration of occupancy, with the exception of the IPECAD model and this analysis; though both used the same source of natural history data (NACC) therefore this may be expected.

This analysis estimates longer time spent in the severe AD state compared to other models in the sample. Minor differences between this analysis and the other models may be explained by the use of 18-month Clarity AD data, differences in natural history data sources used across models, differences in baseline characteristics of the cohort (e.g. age), and the influence of differing mortality data and assumptions. The details of each model, their main data sources, and main assumptions, are detailed by Handels et al.[237]

The Mild AD scenario included four models. The same settings are applied to the model as in the MCI approach aside from the starting population (Table 74).

Table 74: Comparison to IPECAD Mild AD scenario B (SoC arm)

	Duration of state occupancy (years)		
Model	Mild AD	Moderate AD	Severe AD
CPEC (201)	4.25	2.03	1.36
CEM (202)	7.86		
ADACE (205)	2.75	1.70	0.94
JUTKOWITZ (203)	1.44	2.49	1.85
This analysis	[redacted]	[redacted]	[redacted]

Abbreviations: AD – Alzheimer's disease; AD ACE – Alzheimer's disease Archimedes condition-event; CEM – Cost-effectiveness model; CPEC – Care Policy and Evaluation Centre; SoC – standard of care.

The variation across all models is higher under scenario B than scenario A, with the duration of state occupancy in mild AD ranging from 1.44 to 4.25 (excluding CEM). This analysis is broadly similar to the four comparator models. Differences may be due to the same components as discussed under scenario A.

Overall, this economic analysis shows comparable results to other published models, particularly those with comparable settings.

B.3.15 Interpretation and conclusions of economic evidence

This economic analysis was conducted to estimate the cost-effectiveness of lecanemab in comparison with SoC for patients with early AD and confirmed Aβ pathology. The analysis utilised an array of data from the randomised Phase III Clarity AD trial including HRQoL data reported by patients and their caregivers, the best available evidence on the natural history of AD for patients with Aβ pathology identified in the literature, and UK specific healthcare resource use.

Consistent with Clarity AD, the analysis estimates that patients treated with lecanemab spend more time in early AD, in which they experience better HRQoL and more independence, and spend less time in moderate and severe AD. Whilst risk of institutionalisation was not measured in Clarity AD, this was indirectly captured through health state residency, and the analysis estimates people treated with lecanemab spend less time in the institutional setting, compared to patients treated with SoC alone. These clinical benefits translate to higher discounted QALYs per patient ([redacted] incremental QALYs).

PSA, OWSA and extensive scenario analyses were conducted to assess uncertainty in the analysis. The mean probabilistic ICER was just [redacted]% lower than the deterministic ICER, indicating that the analyses are robust despite uncertainty in the input parameters.

The two parameters yielding the biggest impact on cost-effectiveness were time to worsening HRs for mild AD and MCI due to AD. The lecanemab compliance and discontinuation rates also fall within the top 10 most sensitive parameters. As discussed in Section B.3.7, the chronic nature of AD means it can take many years for patients to progress through the various stages of disease, beyond the 18-month timeframe of Clarity AD. Moreover, time-on-treatment for lecanemab is uncertain due to the absence of a stopping rule in Clarity AD and the current lack of consensus among UK clinical experts regarding exactly which stopping rule(s) will be applied in clinical practice. [redacted]

Overall, the scenario analyses results indicate that the base case assumptions are likely conservative, as [redacted]% of the scenarios resulted in a lower ICER than the base case. In most scenarios, there was limited variation in incremental QALYs versus the base case, with incremental QALYs increasing in [redacted]% of scenarios, and remaining the same as the base case in a further [redacted] scenarios. In the scenario using global CDR to define health states and the lecanemab treatment effect, incremental QALYs increased by [redacted] resulting in an ICER of [redacted]. Global CDR was noted by clinicians at the UK HTA advisory board (July 2023) as being a relevant alternative measure of AD progression, however it was not used in the base case as no associated natural history data were identified.

Adopting lower baseline ages of 60 and 65 years also decreases the ICER by [redacted] and [redacted], respectively. For MCI due to AD patients specifically, adopting a baseline age of 65 years reducing the ICER for this subpopulation by [redacted]. These results are relevant as access to diagnostic testing is expected to improve and diagnoses occur earlier over time (a priority in the UK Government's Major Conditions Strategy 2023). Moreover, the potential for blood-based biomarkers which may detect AD 3.5 years prior to clinical diagnosis may lead to patients starting treatment at a younger age and a greater proportion during MCI due to AD.[318,319]

[redacted]Currently, there is no consensus among UK clinical experts regarding exactly which stopping rule(s) will be applied in clinical practice, however it is anticipated that additional stopping rules may be applied in addition to those presented.[61] The addition of such stopping rules could reduce acquisition, administration, and monitoring costs associated with lecanemab. This feedback has also been shared with NHS England and it is expected that discussions regarding a stopping rule for lecanemab in NHS practice will continue in parallel to this appraisal.

As discussed in Section B.3.13, the most appropriate method to apply caregiver utility in cost-effectiveness analyses is not defined in the NICE reference case, and whilst the utility decrement method is the most commonly used, this approach disadvantages treatments in economic analysis which extend life.[320] The considerable reduction in the ICER in this scenario ([redacted] to £[redacted] per

QALY gained) highlights the likely conservative nature of the base case, suggesting that the caregiver QALYs estimated through the decrement approach used in the base case likely underestimate the HRQoL benefits for caregivers associated with introduction of a DMT such as lecanemab, that prolongs the life, independence, and cognitive function of their loved ones.

Despite the extensive published literature on AD, key data gaps remain, including:

- Natural history data specific to the UK; no appropriate UK-specific sources were identified via the SLR. The chosen natural history source was based on NACC data from patients in the US. Whilst not specific to the UK, these data were based on a population with confirmed amyloid beta pathology, thus matching the decision problem, covered the entire AD spectrum, and defined health states using CDR-SB, and were therefore deemed the best available data.

- The available literature to inform UK resource use costs associated with AD is scarce. The Alzheimer's Society report was published almost 10 years ago and may therefore not accurately reflect the extent of the burden of AD to the healthcare system.[283] However, it provides a comprehensive UK-based study across all dementia health states and was therefore the most appropriate source identified. Inputs for MCI due to AD are scarce and were not available from the Alzheimer's Society report hence were derived using a US-based publication, inducing further uncertainty.

- Clarity AD was an 18-month trial, hence extrapolation of the efficacy data were required (Section B.3.3.1.2). It is expected that the ongoing OLE study will provide further insights on the effect of lecanemab beyond 18 months.

Overall, this economic analysis demonstrates lecanemab could materially benefit AD patients and caregivers in comparison to SoC based on extended time in early AD and reduced time in more severe health states which are associated with increased mortality and poorer HRQoL. Given the acute need for a DMT in early AD, there is a clear place for lecanemab in the NHS pathway based on the compelling clinical effectiveness (Section B.2) and long-term effectiveness estimated by the economic analysis.

Importantly, lecanemab is also expected to generate benefits that are not captured in the QALY framework, therefore the cost-effectiveness estimates may underestimate the true value of lecanemab to society. It is widely recognised that survival and quality of life by themselves may not adequately capture all the relevant elements of value in AD, including the value of hope and scientific spillovers, which are difficult to quantify at present.[321] This would represent a paradigm shift in the treatment of

dementia, offer hope to patients and carers, and similar to the value of the first treatments for HIV or multiple sclerosis, could also herald investment in AD and development of new therapeutic agents and targets.

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

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

Company evidence submission – addendum

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B.1 Introduction

Following receipt of the External Assessment Group (EAG) report and completion of the factual accuracy check, the company has opted to submit an updated base case and associated economic analysis for consideration at the first appraisal committee meeting (ACM) on 9th May 2024.

The updated base case adopts a number of EAG preferred settings that the company agree are reasonable, with the aim of resolving some of the EAG's key issues, including:

- Key issue 1 (B.2.1) The cost of amyloid beta (Aβ) testing has been included for all tested patients, not just those treated.
- Key issue 14 (B.2.2): The hazard ratio (HR) for mortality in the MCI due to AD health state has been set equal to general population mortality.
- Key issue 16 (B.2.3): A mixed model for repeated measures (MMRM) has been used to generate health state utility values.
- Key issue 18 (B.2.4): Adverse event (AE) disutilities have been included, combined with AE durations observed in Clarity AD.

One further change has been made to MRI monitoring frequency (B.2.5), to align with the most recent draft Summary of Product Characteristics (SmPC), dated March 2024.[1]

Finally, four additional scenario analyses are presented in Section B.3:

- [redacted].
- adopting the costs used in the NHS England Alzheimer's MCI model, shared alongside the EAG report (key issue 19).
- inclusion of *APOE4* testing for a proportion of patients, aligning with the NICE budget impact test (BIT) and the most recent draft SmPC, dated March 2024, [redacted][1] (key issue 9).
- including a utility cap to reflect general population utility norms (key issue 16).

B.2 Updated company base case

B.2.1 Aβ testing costs

To resolve EAG key issue 1, the cost of Aβ testing has been included for all patients tested in the base case, including those who are amyloid negative and therefore ineligible for treatment, thus not captured in the model cohort. As per the scenario presented by the company in response to clarification question B20, testing costs have been increased in line with the screening failure rate for Aβ positivity in Clarity AD (where 28.80% of patients failed the Tier 5 screening for Aβ pathology).[2] The company note a correction to the formula implemented by the EAG in their model and confirm this correction has been adopted in the updated base case. The following formula is used to calculate Aβ testing costs:

$$Mean\ diagnostic\ testing\ unit\ cost * (\frac{1}{1 - 0.288})$$

The resulting expected cost of diagnostic testing (with amyloid PET of CSF) is presented in Table 1:, with changes shown in ***bold and italic***.

Table 1: Diagnostic testing costs included in the model

Total cost, diagnostics	**Company submission**	**Updated base case**
	£305.91	***£429.65***

B.2.2 Mortality

To resolve EAG key issue 14, the company have assumed a hazard ratio (HR) of 1 for mortality in the MCI due to AD health state. This is applied to the age- and sex-adjusted estimates of general population mortality, based on the Office for National Statistics 2022/2023 life tables for England and Wales (Table 2, changes shown in ***bold and italic***).[3]

The EAG consulted a clinical expert who considered Crowell et al. as an appropriate source for mortality estimates. As such, no changes have been made to the choice of model nor the HRs in other health states.

Table 2: Mortality hazard ratios by AD health state included in the model

Health state	Hazard ratio			
	Company submission	**Source**	**Updated base case**	**Source**
MCI due to AD	0.63	Crowell et al. 2023[4]	***1.00***	*Assumption*
Mild AD	2.43		2.43	Crowell et al. 2023[4]
Moderate AD	3.77		3.77	
Severe AD	8.53		8.53	

AD – Alzheimer's disease; MCI – Mild cognitive impairment

B.2.3 Health state utility values

B.2.3.1 Mixed model for repeated measures

As requested by the EAG to help resolve key issue 16, a multivariable mixed model for repeated measures (MMRM) has been used to estimate health state utility values from Clarity AD. In line with the methodology presented in CS Document B, health states were defined according to CDR-SB and utilities were estimated for patients (self-reported and patient-by-proxy) and caregivers (self-reported).

B.2.3.1.1 Methods

The backward elimination approach was taken to identify the best-fitting model for EQ-5D UK 3L-applied utility index scores for each response type (patient self-reported, patient-by-proxy, and caregiver self-reported). Initially, the following independent variables were modelled as fixed effects:

- baseline EQ-5D utility index score
- treatment group
- use of AD symptomatic medication at baseline
- *APOE4* carrier status
- geographical region
- health state defined by CDR-SB at the time of observation

- presence of treatment-emergent infusion-related reactions, ARIA-E, or ARIA-H (any grade) at the time of observation.

An unstructured covariance matrix was employed to model the covariance of within-patient effect. At each iteration, the variable with the highest p-value was removed from the model, and a new model was fitted. This process was repeated until all variables in the model had a p-value below 0.1. The statistical models tested in the backward elimination process for patient self-reported, patient-by-proxy, and caregiver self-reported responses are summarised in Table 3, Table 4, and Table 5, respectively.

The list of candidate covariates included pre-specified stratification variables in Clarity AD (i.e., use of AD symptomatic medication at baseline, *APOE4* carrier status, and geographical region) and other features of the economic model (i.e., treatment group, health state defined by CDR-SB, presence of adverse events). Note that clinical subgroup was not separately included as a covariate in the model even though it was a stratification variable in Clarity AD, considering that clinical staging can be predicted through the variable 'health state defined by CDR-SB at the time of observation.'

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

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

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

Table 4: Summary of tested models - EQ-5D-3L UK, patient-by-proxy

Covariates	Model Number		
	1	2	3

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

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

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

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

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

MMRM assumes that missing data are missing at random and would have followed the same trend in the remaining patients with same characteristics (e.g. same treatment group). No imputation was performed. Those in the "severe AD" health state defined by CDR-SB were not included in the analysis, given the small sample size. Patients not assigned to a CDR-SB health state, i.e. those with missing CDR-SB data at a given observation, were not included in the analysis given EQ-5D data could not be assigned to a health state.

Model coefficients, standard errors, confidence intervals, and p-values were generated to calculate the MMRM-derived utility scores, and the variance-covariance matrix developed for probabilistic sensitivity analysis. The AIC and BIC diagnostic statistics and variables were reported to inform goodness of fit for each model.

B.2.3.1.2 Patient-reported EQ-5D

A total of [redacted] EQ-5D patient-reported observations from [redacted] individuals in the intent-to-treat Full Analysis Set (ITT FAS+) dataset were available from the Clarity AD core study dataset for the MMRM analysis. Only the patients with assessments available at baseline and at least one post-baseline visit (excluding those in the "severe AD" health state defined by CDR-SB, and those not assigned to a health state due to missing CDR-SB data) were considered for the MMRM utility analysis. Missing data were handled by MMRM as described in the methods section.

Coefficients and statistical significance of each variable are provided in Table 6; 'presence of treatment-emergent IRR, ARIA-E, or ARIA-H at the time of observation' (p=[redacted]) was eliminated from Model 1, 'Use of AD symptomatic medication at baseline' (p=[redacted]) was eliminated from Model 2, and '*APOE4* carrier status' (p=[redacted]) was eliminated from Model 3, as they did not meet the p<0.1 threshold.

Table 6: Coefficients from tested models – EQ-5D-3L UK, patient self-reported

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

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

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

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

In the final MMRM model for self-reported EQ-5D for patients (Model 4), baseline EQ-5D utility index score, treatment group, geographical region, and health state defined by CDR-SB at the time of observation were included. Results suggested treatment with lecanemab was associated with a statistically significant increase in EQ-5D utility score (coefficient=[redacted], p=[redacted]) based on the p-value utilised in the backward elimination process.

Notably, the mild AD health state was associated with a higher EQ-5D index score ([redacted] [moderate AD as reference], p=[redacted]) than MCI due to AD ([redacted] [moderate AD as reference], [redacted]). A similar trend was observed in the meta-analysis by Landeiro et al. 2020[5] which illustrates that while patient-by-proxy EQ-5D utility scores decreased as patients progressed from MCI due to AD to mild AD, patient-reported EQ-5D utility scores remained relatively constant.

Goodness-of-fit statistics for all models tested for patient self-reported EQ-5D values are provided in

Table **7**. Model 4, the most parsimonious model, provided the lowest AIC and BIC scores.

Table 7: Goodness of fit statistics – EQ-5D-3L, patient self-reported

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

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

At baseline, the mean index score derived from patient self-reported EQ-5D for the ITT population was [redacted] (n=[redacted]). The coefficients estimated in Model 4 were applied to the baseline EQ-5D index score to generate MMRM-derived utility scores (Table 8).

Table 8: MMRM-derived health state utility scores, patient self-reported

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

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

B.2.3.1.3 Patient-by-proxy EQ-5D

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

Coefficients and statistical significance are provided in Table 9 for the models tested for patient-by-proxy EQ-5D. As illustrated in the table, 'presence of treatment-emergent IRR, ARIA-E, or ARIA-H at the time of observation' (p=[redacted]) was eliminated from Model 1 and 'Use of AD symptomatic medication at baseline' (p=[redacted]) was eliminated from Model 2 as they did not meet the p<0.1 threshold. In the final MMRM model for patient-by-proxy EQ-5D (Model 3), baseline EQ-5D utility index score, treatment group, *APOE4* carrier status, geographical region, and health state defined by CDR-SB were included.

Table 9: Statistical outputs from tested models – EQ-5D-3L UK, patient-by-proxy

Variable	Model Number		
	1	2	3
Baseline EQ-5D utility index score†	[redacted]***	[redacted]***	[redacted]***
LEC10-BW (vs placebo)	[redacted]*	[redacted]*	[redacted]*
Use of AD symptomatic medication at baseline – No (vs yes)	[redacted]	[redacted]	
APOE4 carrier status (vs non-carrier)	[redacted]*	[redacted]*	[redacted]
Geographical region – Asia-Pacific (vs North America)	[redacted]*	[redacted]*	[redacted]*
Geographical region – Europe (vs North America)	[redacted]*	[redacted]*	[redacted]*

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

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

Results suggested treatment with lecanemab was associated with a statistically significant increase in EQ-5D utility score. *APOE4* carriers had a lower EQ-5D utility score than *APOE4* non-carriers ([redacted], p=[redacted]). Unlike the patient self-reported results, less severe health states were associated with higher EQ-5D utility scores, as would be expected, with the coefficients decreasing with increasing AD severity (MCI due to AD: [redacted]; mild AD: [redacted] [moderate AD as reference], all p<[redacted]).

Model goodness-of-fit statistics for all models tested for patient-by-proxy EQ-5D are provided in Table 10. Model 3, the most parsimonious model, provided the lowest AIC and BIC scores.

Table 10: Goodness of fit statistics – EQ-5D-3L UK, patient-by-proxy

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

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

At baseline, the mean index score derived from patient-by-proxy EQ-5D for the ITT population was [redacted] (n=[redacted]). The coefficients estimated in Model

3 were applied to the baseline EQ-5D index score to generate MMRM-derived utility scores (Table 11).

Table 11: MMRM-derived health state utility scores, patient-by-proxy

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

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

B.2.3.1.4 Caregiver EQ-5D

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

Coefficients and statistical significance are provided in Table 12 for the models tested for caregiver reported EQ-5D. As illustrated in the table, treatment group (p=[redacted]) was eliminated from Model 1, 'Use of AD symptomatic medication at baseline' (p=[redacted]) was eliminated from Model 2, and 'presence of treatment-emergent IRR, ARIA-E, or ARIA-H at the time of observation' (p=[redacted]) was eliminated from Model 3, as they did not meet the $p<0.1$ threshold. Neither 'Use of AD symptomatic medication at baseline' nor 'presence of treatment-emergent IRR, ARIA-E, or ARIA-H at the time of observation' was observed to have statistically significant effect on EQ-5D scores reported by patient or patient-by-proxy.

Table 12: Statistical outputs from tested models – EQ-5D-3L UK, by caregiver

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

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

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

In Model 4, baseline EQ-5D utility index score, patient *APOE4* carrier status, geographical region, and patient health state defined by CDR-SB were included. Less severe health states defined by patient CDR-SB were also associated with higher EQ-5D utility scores for caregivers, with the coefficients decreasing across AD severity levels (MCI due to AD: [redacted], p=[redacted]; mild AD: [redacted], p=[redacted] [moderate AD as reference]).

Model goodness-of-fit statistics for all models tested for caregiver EQ-5D are provided in Table 13. Model 4, the most parsimonious model, provided the lowest AIC and BIC scores.

Table 13: Goodness of fit statistics – EQ-5D-3L UK, by caregiver

Model	N	Log Likelihood	df	AIC	BIC
M1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
M2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

M3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
M4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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

At baseline, the mean index score derived from caregiver self-reported EQ-5D was [redacted] (n=[redacted]). The coefficients estimated in Model 4 were applied to the baseline EQ-5D index score to generate MMRM-derived utility scores (Table 14).

Table 14: MMRM-derived health state utility scores, caregiver

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

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

B.2.3.1.5 MMRM-derived health state utilities

The MMRM-derived health state utility values used in the updated base case for patients and for caregivers compared with the values used in the CS are presented in Table 15 and Table 16, respectively. Values used in the base case (MMRM-derived patient-by-proxy values for patients and MMRM-derived caregiver utilities) are shown in ***bold and italic***.

Although the NICE reference case is to use patient-reported utilities, patient-by-proxy utilities were preferred in the base case due to the counterintuitive results observed for the patient-reported MMRM. The use of patient-by-proxy utilities for all health states is supported by one clinician's feedback in the UK HTA advisory board (July 2023), stating patient-by-proxy utilities should be used at all stages of dementia i.e., for all health states[7], as detailed in response to clarification question B19.

Table 15: Comparison of health state utility values (mean vs. MMRM) for patients – patient self-reported and patient-by-proxy

Health state	Company submission				Updated base case			
	Clarity AD mean utilities (patient)		Clarity AD mean utilities (patient-by-proxy)		Clarity AD MMRM-derived utilities (patient)*		Clarity AD MMRM-derived utilities (patient-by-proxy) **	
	Lecanemab	SoC	Lecanemab	SoC	Lecanemab	SoC	Lecanemab	SoC
MCI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mild AD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

AD – Alzheimer's disease; MCI – Mild cognitive impairment; MMRM – Mixed model for repeated measures SoC – Standard of care
*Covariates used: baseline EQ-5D, treatment group, geographical region, health state (defined by CDR-SB)
**Covariates used: baseline EQ-5D, treatment group, *APOE4* carrier status, geographical region, health state (defined by CDR-SB)

Table 16: Comparison of health state utility values (mean vs. MMRM) for caregivers

Health state	Company submission		Updated base case	
	Clarity AD mean utilities (caregiver)		Clarity AD MMRM-derived utilities* (caregiver)	
	Lecanemab	SoC	Lecanemab	SoC
MCI	[redacted]	[redacted]	[redacted]	[redacted]
Mild AD	[redacted]	[redacted]	[redacted]	[redacted]

AD – Alzheimer's disease; MCI – Mild cognitive impairment; MMRM – Mixed model for repeated measures SoC – Standard of care
*Covariates used: baseline EQ-5D, APOE-4 carrier status, geographical region, health state defined by CDR-SB

B.2.4 Adverse event disutilities

To resolve key issue 18, AE disutilities have been included in the updated base case for serious and severe AEs. This scenario was presented by the company at clarification stage in response to question B15, with durations of AE disutilities informed by clinical expert opinion. Specifically, the duration of ARIA-H and ARIA-E was assumed to be 5-7 days, based on the duration of hospitalisation. The duration of IRR was assumed to be 2-4 hours based on the same clinician's feedback that symptoms would last for 2-4 hours. The median AE durations were taken for each of these AEs.[7]

The EAG requested that the company explore longer durations for AE disutilities, based on their clinical expert feedback in the EAG report: *"The EAG-consulted*

clinical expert highlighting that stabilisation or resolution (of ARIA) typically takes 4-12 weeks. The clinical expert further suggested that, while most infusion-related reactions associated with lecanemab are brief and of low severity, grade 3+ infusion-related reactions would imply severe and prolonged reactions, potentially requiring hospitalisation for monitoring and life-threatening consequences and need for prophylactic treatment if further lecanemab dosing is considered".

The company chose not to model the duration of ARIA-E, ARIA-H, and IRR observed in Clarity AD in the AE disutility scenario presented in response to clarification questions, as use of mean AE durations from Clarity AD may overestimate disutility durations and therefore the associated AE QALY decrements. For IRR, the median durations were 2.5 days and 2.0 days for lecanemab and placebo, respectively. For ARIA-E and ARIA-H, these events typically stabilise before resolution; therefore, the duration of the symptoms (if any) and associated disutility is unlikely to be constant throughout the course of the ARIA event from onset to stabilisation to resolution.

However, to accommodate the EAGs request to explore longer durations, these durations have been used in the updated base case, with the AE disutility being applied for the full duration of ARIA events from onset through to resolution (Table 18, base case shown in ***bold and italic***).

The duration of each event has been calculated as the weighted average of the mean duration observed in each arm of Clarity AD (Table 17).

Table 17: Durations of AEs in Clarity AD

AE	Placebo		Lecanemab		Source
	N	Mean duration (days)	N	Mean duration (days)	
IRR	[redacted]	[redacted]	[redacted]	[redacted]	Ad-hoc biostats output, Table 14.3.1.3.9 [8]
ARIA-E	[redacted]	[redacted]	[redacted]	[redacted]	
ARIA-H	[redacted]	[redacted]	[redacted]	[redacted]	

AE – Adverse event; IRR – Infusion-related reaction; ARIA-E – amyloid-related imaging abnormality-oedema/effusion; ARIA-H – amyloid-related imaging abnormality-microhaemorrhage and haemosiderin deposit
Note: A treatment-emergent AE (TEAE) is defined as an AE that emerged during treatment or within 30 days following the last dose of study drug, having been absent at pretreatment (Baseline) or reemerged during treatment, having been present at pretreatment (Baseline) but stopped before treatment, or worsened in severity during treatment relative to the pretreatment state, when the AE was continuous.
Duration of TEAE (days) = end date of TEAE - start date of TEAE + 1. If no end date due to ongoing AE, it was imputed using the previous date of open-label extension (OLE) first infusion for OLE enrolled subjects or the last visit date in Core Study for not OLE enrolled subjects.

Table 18: AE disutilities included in the model

Adverse event Severity	**Disutility**	**Source**	**Duration (days)**	**Source**	**Disutility**	**Source**	**Duration (days)**	**Source**
	EAG clarification scenario				**Updated base case**			
IRR								
Severe	0.01	Boye et al. 2011[9]	0.125	Eisai LTD. [Data on file] UK clinical expert opinion. 2023[10]	0.01	Boye et al. 2011[9]	[redacted]	Values calculated from Table 14, based on ad-hoc biostats output, Table 14.3.1.3.9.[8]
Serious	0.01		0.125		0.01		[redacted]	
ARIA-E								
Severe	0.0266	Sullivan et al. 2006[11]	6	Eisai LTD. [Data on file] UK clinical expert opinion. 2023[10]	0.0266	Sullivan et al. 2006[11]	[redacted]	Values calculated from Table 14, based on ad-hoc biostats output, Table 14.3.1.3.9.[8]
Serious	0.0266		6		0.0266		[redacted]	
Isolated ARIA-H								
Severe	0.1	Meckley et al. 2010[12]	6	Eisai LTD. [Data on file] UK clinical expert opinion. 2023[10]	0.10	Meckley et al. 2010[12]	[redacted]	Values calculated from Table 14, based on ad-hoc biostats output, Table 14.3.1.3.9.[8]
Serious	0.1		6		0.10		[redacted]	

AE – Adverse event; IRR – Infusion-related reaction; ARIA-E – amyloid-related imaging abnormality-oedema/effusion; ARIA-H – amyloid-related imaging abnormality-microhaemorrhage and haemosiderin deposit

B.2.5 Frequency of MRI monitoring

To align with the most recent draft SmPC, the number of MRIs required in year 1 of treatment in the model has been updated.[1]

In the original CS, patients were assumed to receive 3.88 MRI scans in year 1 as advised by clinical expert opinion from the UK HTA advisory board (July 2023). The most recent draft SmPC states that patients should [redacted]. The base case analysis has therefore been updated accordingly to assume [redacted] MRI scans in year 1.

The draft SmPC does not specify the number of MRIs required beyond the first year of treatment, therefore no changes have been made to assumptions for MRI monitoring frequency in years 2 and beyond.

B.3 Additional scenario analyses

B.3.1 Lecanemab treatment duration

A scenario analysis is presented using the updated base case, in which it is assumed that [redacted].

[redacted]. In the CS base case, the all-cause discontinuation rate observed in Clarity AD was extrapolated beyond the 18-month core study follow-up to align with the NICE reference case, as the trial did not include a stopping rule and the draft SmPC (at the time of submission) stated [redacted]

[redacted]

As described in the CS, Document B, Section B.2.6.2.1, amyloid PET, as measured by Centiloids (CL), was reduced from the baseline amyloid PET level of 77.9 CL to [redacted] CL in the lecanemab arm at the end of the Clarity AD core study (i.e. 18

months). This is below the 30 CL threshold for amyloid negativity in Clarity AD, which is considered a 'normal' level, above which participants are considered to have elevated or 'higher than normal' brain amyloid.[13] [redacted]

B.3.2 NHS England Alzheimer's MCI model costs

An additional scenario is included in which unit costs and frequencies (where applicable) for administration, diagnosis, referral, monitoring, and *APOE4* testing costs in the analysis align with the NHS England Alzheimer's MCI model.

The EAG highlighted in key issue 19 a number of discrepancies between the company's economic model and the NHS England Alzheimer's MCI model. As detailed in the factual accuracy response, the company is concerned that the sources used in the NHS England Alzheimer's MCI model are unclear, with the majority of costs not being referenced, and others referencing input obtained via email with individual clinicians/NHS England employees, rather than consensus from a group of clinicians, or not utilising NHS reference costs where available. Consequently, the company consider the unit costs adopted in the CS base case to be the more appropriate costs available. Table 19 details the discrepancies between the CS base case and the NHS England model.

Table 19: Cost and resource use comparison: CS model vs NHS England Alzheimer's MCI model

Cost/resource use	Company model	Reference	NHS England Alzheimer's MCI model	Reference in NHSE model
Unit cost lecanemab administration IV infusion per visit	£207.59	National Schedule of NHS Costs 2021/22 (Deliver Simple Parenteral Chemotherapy at First Attendance, outpatient, SB12Z)	£565.00	NR*
Unit cost lumbar puncture	£295.80	National Schedule of NHS Costs 2021/22 (Outpatient procedure diagnostic spinal puncture, 19 years and over, neurology service, HC72A, service code 401)	£580.00	[redacted]
Unit cost PET-CT	£396.94	National Schedule of NHS Costs 2021/22, weighted average of outpatient PET scan (RN01A, RN07A)	£1000.00	[redacted]
Aβ testing: ratio CSF:PET CT	90%:10%	Clinical opinion. UK HTA advisory board, July 2023	85%:15%	NR
MRI safety monitoring	Average of 3.88 MRIs in year 1 and 1.13 in years 2, 3, and 4	UK HTA advisory board report. July 2023.	MRIs in intervals of 13 weeks	[redacted]
GP visit	Not included	N/A	3 visits (total cost of £75.00)	NR
Quarterly outpatient review	Not included	N/A	Every 13 weeks (£350 each)	NR
APOE4 test	Not included	N/A	Unit cost of £250	NR

		N/A	Outpatient appointment: unit cost of £200	NR
		N/A	Counselling: unit cost of £350	NR
Referral to local services (e.g., memory clinics)	Not included	N/A	Unit cost: £400	NR

Adapted from EAG report Table 4.18
*NHSE reference WD02Z (Alzheimer's Disease or Dementia, treated by a Non-Specialist Mental Health Service Provider), however, the unit costs used in the model does not align with any of the costs under code WD02Z in National Schedule of NHS Costs 2021/22.
APOE4 = apolipoprotein E4; CSF = cerebrospinal fluid; GP = general practitioner; IV = intravenous; MCI = mild cognitive impairment; MRI = magnetic resonance imaging; N/A = not applicable; NHS = National Health Service; NR = not reported; PET-CT = positron emission tomography computed tomography

B.3.3 *APOE4* testing

In the latest draft SmPC, [redacted]. However, it is not a requirement for treatment with lecanemab, and is not currently routinely tested in UK clinical practice. In the latest budget impact test for this appraisal, it is assumed that [redacted]% of patients undergo *APOE4* testing prior to treatment with lecanemab. This aligns with clinical feedback obtained by the company at clarification stage, indicating that *APOE4* testing would not be mandatory and only a proportion of patients would undergo testing, due to the genetic implications. As such, [redacted]% of patients are assumed to undergo *APOE4* testing in this scenario.[15]

B.3.4 General population utility cap

In line with the alternative approach suggested by the EAG to resolve key issue 16, the health state utility value for the lecanemab MCI due to AD health state has been capped at UK age- and sex- matched general population values, following the approach recommended by Hernandez Alava et al., 2022.[16] The multiplier required to cap the lecanemab MCI utility at the age- and sex- matched utility value is applied to the SoC MCI utility value, to maintain treatment differences observed in the MMRM-derived utilities. The health state utility values for subsequent health states are calculated as relative decrements vs. the previous health state to maintain between-health state differences observed in the MMRM-derived utilities. As such, health state utility values cannot exceed general population norms in any health state when varied in probabilistic sensitivity analysis.

B.4 Summary of updates

Table 20 summarises all updates that have been made to the model base case and scenarios.

Table 20: Summary of model updates

Updated component	Update	Section
Base case updates		
Aβ testing costs	Include cost of Aβ testing for all patients tested	B.2.1
Mortality	Amended in the MCI due to AD health state to align with the UK general population	B.2.2
Utilities	Use MMRM to estimate health state utilities rather than mean values	B.2.3.1.5
AE disutilities	Included for serious and severe AEs.	B.2.4
Additional scenarios		
Lecanemab treatment duration	[redacted]	B.3.1
Costs	Unit costs aligned with the NHS England Alzheimer's MCI model	B.3.2
APOE4 testing	Testing is assumed for a proportion of patients	B.3.3
Utilities	Health state utility values have been capped at UK age- and sex- matched general population values.	B.3.4

Aβ - amyloid beta; AD – Alzheimer's Disease; AE – adverse event; MCI – mild cognitive impairment; MMRM - Mixed Model for Repeated Measures; MRI – magnetic resonance imaging; NHS – National Health Service; SmPC – Summary of Product Characteristics; UK – United Kingdom

B.5 Updated base-case results

B.5.1.1 Base-case incremental cost-effectiveness analysis results

B.5.1.1.1 Incremental benefits

In the updated company base case, the economic analysis estimates a slower rate of disease progression for lecanemab compared with SoC, as observed in Clarity AD. Specifically, treatment with lecanemab delays onset of moderate AD by [redacted] years. Consequently, patients treated with lecanemab spend more time in early AD ([redacted] incremental LYs) and less time in moderate and severe AD ([redacted] incremental LYs), compared to patients treated with SoC alone. The estimated mean time on treatment with lecanemab is [redacted] years based on the stopping rules described in the CS, Document B, Section B.3.3.3.3.

Lecanemab also indirectly reduces the risk of institutionalisation through slowing of disease progression to more severe health states in which risk is higher. Lecanemab therefore increases the time patients spend in community care ([redacted] incremental LYs) and reduces time spent in institutional care compared with SoC ([redacted] vs. [redacted] years, respectively).

Overall, these benefits of lecanemab translate to a survival benefit of [redacted] years due to the delayed time to more severe stages of AD with associated increased mortality. Similarly, lecanemab generates an increase in discounted QALYs of [redacted] versus SoC due to the relatively greater time spent in early AD in community care, which has multiple HRQoL benefits for patients and their caregivers.

B.5.1.1.2 Incremental costs

Costs associated with lecanemab (including acquisition, administration, diagnostic testing, monitoring, and management of AEs) were partially offset by reductions in direct medical costs (-£[redacted]) and direct non-medical care costs (-£[redacted]) versus SoC. The primary drivers of the incremental costs (£[redacted]) associated with lecanemab are the acquisition and administration costs given the low cost of orally-administered SoC symptomatic treatments.

B.5.1.1.3 Incremental cost-effectiveness

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

Table 21: Base-case results

Technologies	Total			Incremental			ICER (per QALY)	NHB at £30,000
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs		
SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lecanemab	[redacted]	[redacted]	[redacted]					

Abbreviations: ICER – Incremental cost-effectiveness ratio; LYG – life years gained; NHB – net health benefit; QALY – quality-adjusted life year; SoC – standard of care

B.6 Sensitivity analyses results

B.6.1.1 Probabilistic sensitivity analysis

Joint parameter uncertainty was explored through PSA, in which all appropriate parameters are assigned distributions and varied jointly. Those not appropriate for variation include structural assumptions (e.g., cell links for model options, time horizon) and those considered to be certain (e.g., drug acquisition costs). A total of 1,000 Monte Carlo simulations were recorded and plotted over time to demonstrate ICER convergence. Results were plotted on the incremental cost-effectiveness plane (Figure 1) and a cost-effectiveness acceptability curve (CEAC) (Figure 2) was generated presenting the percentage of simulations in which lecanemab is cost-effective over willingness-to-pay (WTP) thresholds from £0-100,000 per QALY gained.

The mean costs and QALYs were comparable to the deterministic base case values, resulting in a probabilistic ICER just £[redacted] lower than the base case ICER (£[redacted], Table 22).

Table 22: PSA base-case results

Technology	Total		Incremental		
	Costs (£)	QALYs	Costs (£)	QALYs	ICER (per QALY)
SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lecanemab	[redacted]	[redacted]			

Abbreviations: ICER – incremental cost-effectiveness ratio; LYG – life years gained; NHB – net health benefit; PSA – probabilistic sensitivity analysis; QALY – quality-adjusted life year; SoC – standard-of care

Figure 1: Incremental cost-effectiveness plane

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

Figure 2: Cost-effectiveness acceptability curve

Abbreviations: SoC - standard of care

B.6.1.2 One-way sensitivity analysis

One-way sensitivity analysis (OWSA) was conducted by varying one parameter at a time and assessing the subsequent impact on cost-effectiveness. By adjusting each parameter individually, the sensitivity of the model results to that parameter can be assessed.

The OWSA was conducted by allocating a 'low' value and a 'high' value to each parameter; the low value is the lower bound of the 95% CI, the high value is the upper bound of the 95% CI**.** In the absence of CI data, the variable was altered by +/- 20%. A OWSA tornado diagram presenting the top ten most sensitive parameters is presented with tabulated results presented in Table 23.

The parameters yielding the biggest impact on cost-effectiveness results are time to worsening HRs for mild AD and MCI due to AD, and the Farina patient-by-proxy health state utility values for mild, moderate, and severe AD. The SEs reported by Farina et al. were very large relative to the means (0.3 for all health states compared with means of 0.7, 0.5, and 0.4, respectively). Therefore, the variation in results is likely attributable to uncertainty in the Farina et al. study, rather than the health state utility values being key drivers of results.

Table 23: Tabulated OWSA results for lecanemab vs SoC

Parameter	Lower bound ICER (£)	Upper bound ICER (£)	Difference (£)
Time to worsening HR, mild AD (CDR-SB)	[redacted]	[redacted]	[redacted]
Utility: Farina (carer as proxy) - Mild AD	[redacted]	[redacted]	[redacted]
Time to worsening HR, MCI due to AD (CDR-SB)	[redacted]	[redacted]	[redacted]
Utility: Farina (carer as proxy) - Severe AD	[redacted]	[redacted]	[redacted]
Lecanemab compliance	[redacted]	[redacted]	[redacted]
Utility: Farina (carer as proxy) - Moderate AD	[redacted]	[redacted]	[redacted]
Discontinuation rate: Clarity, all cause - lecanemab	[redacted]	[redacted]	[redacted]
Lecanemab cost of administration (company)	[redacted]	[redacted]	[redacted]
Caregiver utility: Black - community - Moderate AD	[redacted]	[redacted]	[redacted]
Potashman, MCI due to AD to mild AD	[redacted]	[redacted]	[redacted]

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

Figure 3: OWSA tornado diagram

Abbreviations: AD - Alzheimer's disease; CDR-SB – Clinical dementia rating – sum of boxes; HR – hazard ratio; ICER – incremental cost-effectiveness ratio; MCI – mild cognitive impairment.

B.6.1.3 Scenario analysis

The scenarios explored are as per Table 69 in the CS, Document B, Section B.3.11.3, excluding those that have been adopted in the updated base case. Additional scenarios explored are presented in Table 24.

The results are generally stable and the ICER improves in most scenarios versus the base case (Table 25), indicating that the base case settings are likely to be conservative. Of note are the lecanemab treatment duration and additive carer utilities scenarios, which both result in a substantial decrease in the ICER. The NHSE Alzheimer's MCI model scenario resulted in a substantial increase in the ICER. The results of the treatment duration and NHSE costs scenarios are discussed in more detail in Sections B.6.1.3.1B.1.1.1.1 and B.6.1.3.2, respectively. Also of note is the scenario including *APOE4* testing for a proportion of patients, increasing the ICER by less than [redacted]

Table 24: Scenarios explored in the cost-effectiveness analysis

Category	Base case	Scenario	
	Value	Value	Rationale
Lecanemab treatment duration	Not applied	[redacted]	[redacted]
Source of unit costs	CS	NHSE model	To explore the impact of unit costs proposed in the NHS England Alzheimer's MCI model.
Inclusion of *APOE4* testing for proportion of patients	0%	[redacted]% patients assumed to undergo *APOE4* testing	As per the NICE BIT and the latest draft SmPC, *APOE4* testing is recommended prior to treatment with lecanemab to inform the risk of developing ARIA. However, *APOE4* testing is not a requirement for treatment with lecanemab, and is not currently routinely tested for in UK clinical practice. As such, it is assumed that only a proportion of patients will undergo testing. This aligns with clinical feedback obtained by the company at clarification stage, and with the NICE BIT, in which [redacted]% patients undergo *APOE4* testing. The proportion in this scenario aligns with the NICE BIT.[15]
Inclusion of AB testing costs	Included for all tested	Included for model cohort	To align with the company submission. Incorporating costs for all patients tested, not just those who are treated with lecanemab, means that costs are captured for patients not treated with lecanemab in the lecanemab arm.
Mortality in MCI health state	Equal to general population (i.e. HR=1)	HR=0.63	To align with the mortality estimates reported by Crowell et al. for other model health states, as used in the company submission.[4]

Category	Base case	Scenario	
	Value	Value	Rationale
Health state utilities for MCI and mild, patient and caregiver	MMRM-derived utilities (caregiver proxy-reported for patients)	MMRM-derived utilities (self-reported for patients)	Alternative source of HSUVs measured through an MMRM model for EQ-5D-3L, in line with the NICE reference case.
		Mean utilities	To compare against the original company submission approach, using patient-reported health state utilities that decrease with increasing disease severity.
Health state utilities	MMRM-derived utilities (caregiver proxy-reported for patients)	Capped at general population	To align with the EAG scenario presented for key issue 16.
AE disutilities	Included for serious and severe only	Not included	The utility analysis using Clarity AD data calculates utility values by treatment arm. As such, this may capture the impact of AEs on HRQoL which is then reflected in the health state utility values, which may mean AE disutility is double-counted in the base case.

Abbreviations: AD – Alzheimer's disease; ARIA – amyloid-related imaging abnormalities; CDR – Clinical Dementia Rating; CDR-SB – Clinical Dementia Rating Scale - Sum of Boxes; DMT – disease modifying therapy; HR – hazard ratio; HTA – health-technology assessment; MCI – mild cognitive impairment; MRI – magnetic resonance imaging; NICE – National Institute for Health and Care Excellence; PSS – Personal social services; QALY – quality-adjusted life year; QoL – quality of life; SLR – systematic literature review; SmPC – Summary of Product Characteristics; UK – United Kingdom

Table 25. Scenario analysis results

#	Scenario	Deterministic ICER	Probabilistic ICER
	Base case	[redacted]	[redacted]
1.	1.5% discount for costs and outcomes	[redacted]	[redacted]
2.	3.5% discount for costs, 1.5% discount for outcomes	[redacted]	[redacted]
3.	Baseline age = 65 years	[redacted]	[redacted]
4.	Baseline age = 60 years	[redacted]	[redacted]
5.	Health state definition: Global CDR	[redacted]	[redacted]
6.	Diagnostic testing costs excluded	[redacted]	[redacted]
7.	No wastage	[redacted]	[redacted]
8.	Switch to natural history data at baseline (0 years)	[redacted]	[redacted]
9.	Assume lifetime lecanemab benefit	[redacted]	[redacted]
10.	Source of institutionalisation probabilities: Belger	[redacted]	[redacted]
11.	Patient health state costs: Excluded for MCI	[redacted]	[redacted]
12.	Unpaid care costs: Included	[redacted]	[redacted]
13.	Unpaid care costs: Included for mild moderate and severe AD, excluded for MCI	[redacted]	[redacted]
14.	Source of patient health state utility values in moderate and severe AD: Landeiro	[redacted]	[redacted]
15.	Caregiver (dis)utility approach: patient and caregiver additive	[redacted]	[redacted]
16.	Caregiver utility source for moderate and severe AD: Mesterton	[redacted]	[redacted]
17.	Caregiver utility source for moderate and severe AD: Lopez-Bastida	[redacted]	[redacted]
18.	Population at baseline: MCI due to AD only	[redacted]	[redacted]
19.	Population at baseline: Mild AD only	[redacted]	[redacted]
20.	Population and age at baseline: MCI due to AD, 65 years	[redacted]	[redacted]
21.	Cap utilities at general population age and gender norms	[redacted]	[redacted]
22.	Align unit costs with NHSE AD MCI model	[redacted]	[redacted]
23.	[redacted]	[redacted]	[redacted]
24.	Exclude AE disutilities	[redacted]	[redacted]
25.	Inclusion of *APOE4* testing for proportion of patients	[redacted]	[redacted]
26.	Health state utilities for MCI and mild, patient and caregiver – MMRM patient reported	[redacted]	[redacted]
27.	Health state utilities for MCI and mild, patient and caregiver – mean utilities	[redacted]	[redacted]
28.	Inclusion of AB testing costs only for those treated with lecanemab	[redacted]	[redacted]
29.	Mortality in MCI health state as per Crowell et al.	[redacted]	[redacted]
30.	Scenarios 15 and 23	[redacted]	[redacted]

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

B.6.1.3.1 Lecanemab treatment duration scenario

When assuming [redacted], the cost-effectiveness of lecanemab compared with SoC is improved with a substantially lower ICER ([redacted]%) than the updated base case ICER, at £[redacted] per QALY gained (Table 26). Lecanemab generates an additional [redacted] QALYs at an additional cost of £[redacted]. This result is driven by the reduced drug acquisition and administration costs, which outweigh the resulting reduction in incremental LYs and QALYs.

[redacted]

Table 26: Lecanemab treatment duration scenario results (deterministic)

Technology	Total			Incremental			ICER (per QALY)
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs	
SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lecanemab	[redacted]	[redacted]	[redacted]				

Abbreviations: ICER – Incremental cost-effectiveness ratio; LYG – life years gained; NHB – net health benefit; QALY – quality-adjusted life year; SoC – standard of care

Table 27: Lecanemab treatment duration scenario results (probabilistic)

Technology	Total		Incremental		ICER (per QALY)
	Costs (£)	QALYs	Costs (£)	QALYs	
SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lecanemab	[redacted]	[redacted]			

Abbreviations: ICER – Incremental cost-effectiveness ratio; LYG – life years gained; NHB – net health benefit; QALY – quality-adjusted life year; SoC – standard of care

B.6.1.3.2 NHS England model cost scenario

Using unit costs and frequencies (where applicable) aligning with the NHSE Alzheimer's MCI model for administration, diagnosis, monitoring, and *APOE4* testing, as detailed in Section B.3.2, the ICER for lecanemab compared with SoC is £[redacted] per QALY gained, a [redacted]% increase from the base case ICER (Table 28). Lecanemab generates an additional [redacted] QALYs at an additional cost of £[redacted].

[redacted]. This is primarily driven by the administration cost, which is assumed to be £565 per infusion in the NHSE Alzheimer's MCI model.

Table 28: NHSE model cost scenario results

Technology	Total			Incremental			ICER (per QALY)
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs	
SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lecanemab	[redacted]	[redacted]	[redacted]				

Abbreviations: ICER – Incremental cost-effectiveness ratio; LYG – life years gained; NHB – net health benefit; QALY – quality-adjusted life year; SoC – standard of care

Table 29: NHSE model cost results (probabilistic)

Technologies	Total		Incremental		ICER (per QALY)
	Costs (£)	QALYs	Costs (£)	QALYs	
SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lecanemab	[redacted]	[redacted]			

Abbreviations: ICER – Incremental cost-effectiveness ratio; LYG – life years gained; NHB – net health benefit; QALY – quality-adjusted life year; SoC – standard of care

B.7 Subgroup analysis

To align with the *APOE4* subgroup analyses presented at clarification stage in response to question A9, the results of subgroup analyses for non-carriers, heterozygotes, and homozygotes with the updated base case settings are presented in Table 30, Table 31, and Table 32, respectively.

Table 30: *APOE4* non-carriers subgroup analysis

Technology	Total			Incremental			ICER (per QALY)
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs	
SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lecanemab	[redacted]	[redacted]	[redacted]				

Abbreviations: APOE4 – apolipoprotein 4; ICER – Incremental cost-effectiveness ratio; LYG – life years gained; NHB – net health benefit; QALY – quality-adjusted life year; SoC – standard of care

Table 31: *APOE4* heterozygous subgroup analysis

Technology	Total			Incremental			ICER (per QALY)
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs	
SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lecanemab	[redacted]	[redacted]	[redacted]				

Abbreviations: APOE4 – apolipoprotein 4; ICER – Incremental cost-effectiveness ratio; LYG – life years gained; NHB – net health benefit; QALY – quality-adjusted life year; SoC – standard of care

Table 32: *APOE4* homozygous subgroup analysis

Technology	Total			Incremental			ICER (per QALY)
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs	
SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lecanemab	[redacted]	[redacted]	[redacted]				

Abbreviations: APOE4 – apolipoprotein 4; ICER – Incremental cost-effectiveness ratio; LYG – life years gained; NHB – net health benefit; QALY – quality-adjusted life year; SoC – standard of care

B.8 Interpretation and conclusions of economic evidence

This updated base case has been submitted to align with the EAG preferred assumptions the company agree are reasonable, with the aim of resolving some of the EAG's key issues and reducing associated uncertainty.

The updated base case results demonstrate that, as per the company submission, lecanemab has a slower rate of disease progression compared with SoC, as observed in Clarity AD. Specifically, treatment with lecanemab delays onset of moderate AD by [redacted] years. Consequently, patients treated with lecanemab spend more time in early AD ([redacted] incremental LYs) and less time in moderate and severe AD ([redacted] incremental LYs), compared to patients treated with SoC alone. Based on a [redacted], the ICER for lecanemab compared with SoC is £[redacted] per QALY gained. Lecanemab generates an additional [redacted] QALYs at an additional cost of £[redacted]

The parameters yielding the biggest impact on cost-effectiveness results in the OWSA were unchanged from the company submission (time to worsening HRs for mild AD and MCI due to AD, and the Farina patient-by-proxy health state utility values for mild, moderate, and severe AD). The mean probabilistic ICER was just [redacted]% lower than the deterministic ICER, indicating that the analyses are robust despite uncertainty in the input parameters.

[redacted]

When caregiver utility is modelled as the absolute HRQoL for both caregivers and patients summed in each cycle rather than as a decrement, the ICER is reduced considerably, by [redacted] to £[redacted] per QALY gained. This highlights the

extent of the potential ‘true’ benefit to caregivers QoL of lecanemab, and indicates the base case approach for modelling caregiver effects is likely to be conservative, given this penalises lecanemab for keeping patients alive as the associated decrement is applied for the extended survival time. When combined with the lecanemab treatment duration scenario, the ICER is further reduced to £[redacted] ([redacted]%) per QALY gained.

In contrast, adopting unit costs, frequencies, and other assumptions from the NHSE Alzheimer’s MCI model results in a [redacted] increase in the ICER, to £[redacted] This is primarily driven by the administration cost, which is assumed to be £565 per infusion in the NHSE Alzheimer’s MCI model, regarding which the company has raised its concerns in factual accuracy response.

Overall, as per the original CS, the updated economic analysis demonstrates that lecanemab could materially benefit early AD patients and their caregivers in comparison to SoC based on extended time in early AD and reduced time in a more severe health state. Given the acute unmet need in early AD, there is a clear place for lecanemab in the NHS pathway based on the compelling clinical effectiveness and long-term effectiveness estimated by the economic analysis. Moreover, benefits that are not captured in the QALY framework mean the cost-effectiveness estimates may underestimate the true value of lecanemab to society.

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

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

Summary of Information for Patients (SIP)

December 2023

File name	Version	Contains confidential information	Date
[ID4043]_Lecanemab_ Summary of information for patients_20Dec23	Final	No	20 December 2023

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: Lecanemab **Brand name:** To be confirmed following approval by the Medicines and Healthcare products Regulatory Agency (MHRA).

1b) Population this treatment will be used by. Please outline the main patient population that is being appraised by NICE:

Lecanemab will be used by people with mild cognitive impairment due to Alzheimer's disease or mild dementia due to Alzheimer's disease (collectively referred to as early Alzheimer's disease).

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 marketing authorisation for lecanemab is pending because the MHRA application is ongoing. Anticipated dates for marketing authorisation are outlined in section B.1.2 of the company submission.

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:

There are no existing collaborations between Eisai and patient groups in relation to lecanemab.

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.

Alzheimer's disease is an illness that affects the brain. Communications between brain cells become blocked due to a build-up of amyloid beta plaques and a protein called tau. This eventually leads to problems with memory, thinking and behaviour. Alzheimer's disease symptoms can be different for everyone. Symptoms usually develop slowly and get worse over time, becoming severe enough to interfere with daily tasks.

The word 'dementia' describes a set of symptoms that over time can affect memory, problem-solving, thinking, language and behaviour. Alzheimer's disease is the most common type of dementia.[1]

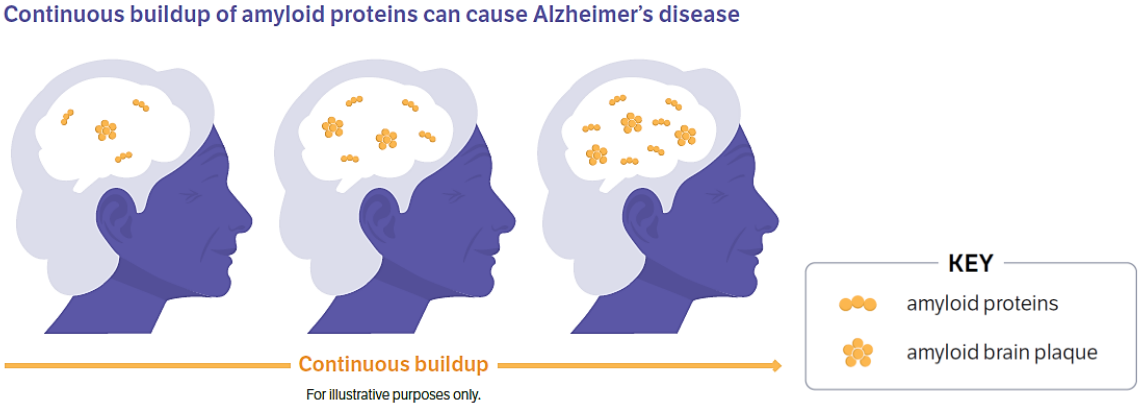
NICE will appraise lecanemab for the treatment of people with early stages of Alzheimer's disease, which are known as:

- **Mild cognitive impairment (MCI) due to Alzheimer's disease**
  This is when symptoms like forgetfulness and confusion are mild and may not get in the way of daily life.

- **Mild dementia due to Alzheimer's disease**
  This is when symptoms like trouble keeping track of bills and difficulty with familiar tasks start to get in the way of daily life.

What causes Alzheimer's disease?

People with Alzheimer's disease have too much of a protein called amyloid beta that continuously builds up in the brain. It starts with small forms of amyloid protein. These may clump together into larger forms, which can damage brain cells. As they continue to build up, they can form harmful amyloid brain plaques.[2]



How many people have the condition?
Research has suggested that one or two people in every 10 over the age of 65 have MCI due to different causes. It is expected that just over half of those people have MCI due to Alzheimer's disease, but because the condition is not always diagnosed it is difficult to know exactly how many people are affected.[3] [4]

In England, around 4 people in every 100 over the age of 65 have dementia due to any reason.[5] Of these, approximately a quarter have dementia due to Alzheimer's disease that is mild in severity.[6] However, many of these will not have been confirmed by biomarker tests. The largest risk factor for dementia is age, with over 95% of all cases in people aged over 65.[7]

Burden of disease
Alzheimer's disease is a progressive brain disease causing difficulties with memory, thinking and language, resulting in symptoms such as memory loss, confusion, and personality changes. As the disease worsens, patients lose their ability to live independently and become completely dependent on others for help with basic activities of daily living in the most severe stage.[8] This places a significant burden on patients affected by Alzheimer's disease and their families and places a financial strain on healthcare and social care systems.[9]

Mortality statistics
Dementia and Alzheimer's disease was the leading cause of death in 2022.[10] In England and Wales, dementia and Alzheimer's disease accounted for almost 66,000 (11.4% of all deaths) in 2022.[11] Dementia is the only major cause of death without a treatment to slow or stop disease progression.[11]

Emotional effects on patients
Most people living with Alzheimer's disease experience problems with their memory and thinking. This can lead to loss of:

- Self-esteem and confidence
- Social roles and relationships
- The ability to carry out hobbies
- Everyday life skills (for example, cooking and driving)

The ability to perform activities of daily living and being independent is an important component of quality of life. A UK-based study found that deteriorating ability to perform activities of daily living had a negative impact on quality of life for patients with moderate dementia.[12]

Impact on carers
Alzheimer's disease also has a substantial impact on the health-related quality of life for carers. At the time of diagnosis, carers report feeling worried, sad and uncertain.[13]

- A 2018 research study conducted by Alzheimer's Society found that 90% of caregivers for people with dementia experience feelings of stress or anxiety several times a week.[14]
- Approximately 40% of those caring for patients with dementia provide constant, "round-the-clock" care. Carers told Alzheimer's Society of how they struggled with exhaustion due to countless sleepless nights, lack of socialising, and neglecting their own health.[14]

- Caregiving can be physically and emotionally challenging, often leaving caregivers with limited opportunities to take breaks or time off from their caregiving responsibilities.[14]

Another study reported that carer health-related quality of life is also negatively impacted by the worsening disease severity of the patient, with a two-fold worsening between the mild and severe stages of Alzheimer's disease.[15]

In the UK, 1.3 billion hours of unpaid care are provided by family and other caregivers each year.[16] A UK study revealed that 87% of people with dementia receive help from family in their day-to-day life, indicating the scale of burden on patients' loved ones.[17]

These studies reflect the burden faced by caregivers, in terms of emotional strain, time spent caring and subsequently the impact on their ability to work.

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?

There is no simple test for Alzheimer's, so it's never possible to be 100% sure of a diagnosis. To be as accurate as possible, the specialist health professional will look at and consider different pieces of information including:[18]

- **a medical 'history'** – the clinician talks to the person, and ideally someone who knows them well, about how their problems have developed and how they are affecting their daily life, for example about changes in their mood or the sort of tasks they are able to do at home.
- **physical examination and tests**, such as blood or urine tests, to check for other possible causes of the person's symptoms.
- **a series of questions** to understand more about memory, awareness of time and place, and how a person thinks things through.
- **a scan of the brain**, if this is needed to make a diagnosis.

Lecanemab works by **targeting amyloid beta proteins** and **reducing amyloid brain plaque**. One criterion for patients taking lecanemab will be confirmation of increased levels of amyloid proteins. Currently, this means that patients will need to have one of these tests to check for amyloid brain plaque.

- **Cerebrospinal fluid (CSF) test**
  - This test takes samples of the fluid around the brain and spinal cord called cerebrospinal fluid or CSF.
  - The CSF is taken using a lumbar puncture, where a thin needle is inserted between the bones in the lower spine. It should not be painful, but the patient may have a headache and some back pain for a few days.[19]
  - It is carried out in hospital by a doctor or specialist nurse.[19]

- **Amyloid positron emission tomography (PET) scan**
  - This test uses a special machine that takes pictures of the brain.
  - PET scanners work by detecting the radiation given off by a substance injected into the arm called a radiotracer as it collects in different parts of the body.[20]
  - A specific radiotracer that detects amyloid will be used in this PET scan.
  - It is carried out in hospital by a specialist radiologist.

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.

For mild cognitive impairment (MCI) due to Alzheimer's disease

- Currently, there is no UK clinical guideline for patients with MCI so there is a wide variation in how these patients are treated.[21]
- No drugs are recommended to treat patients with MCI due to Alzheimer's disease.

For mild dementia due to Alzheimer's disease

- Doctors primarily follow the NICE guideline for assessment and management of dementia (NG97), which recommends drug and non-drug treatments.[22]
- At present, approved drug treatments are donepezil, galantamine, rivastigmine and memantine.
  - NICE recommends either donepezil, galantamine or rivastigmine (which are a type of drug called acetyl cholinesterase (AChE) inhibitors) for mild to moderate Alzheimer's disease.
  - It is important to note that these drug treatments only provide temporary relief of symptoms, they do not treat the underlying cause of Alzheimer's disease.

The table below summarises the drug treatments for managing different stages of Alzheimer's disease, as outlined in the NICE dementia guideline (NG97).

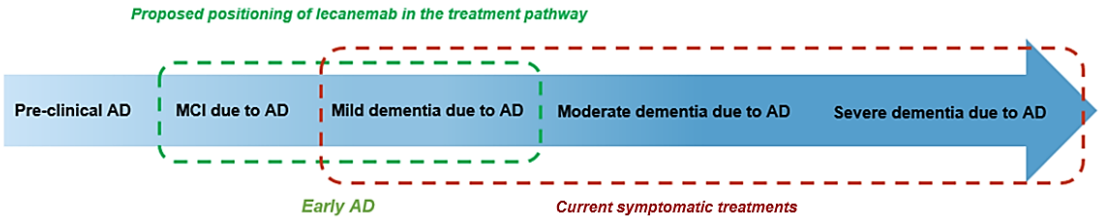
<table>
<tr><th>MCI due to AD</th><th>Mild dementia due to AD</th><th>Moderate dementia due to AD</th><th>Severe dementia due to AD</th></tr>
<tr><td rowspan="2">No guideline available</td><td rowspan="2">AChE inhibitors:
• Donepezil
• Galantamine
• Rivastigmine</td><td>AChE inhibitors:
• Donepezil
• Galantamine
• Rivastigmine

For patients who are unable to take AChE inhibitors:
• Memantine</td><td>NMDA receptor antagonists:
• Memantine</td></tr>
<tr><td colspan="2">For patients with an established AD diagnosis:
• AChE inhibitor + memantine</td></tr>
</table>

Source: NICE Guideline NG97[22]
AChE: Acetyl cholinesterase; AD: Alzheimer's disease; MCI: Mild cognitive impairment; NMDA: N-methyl-D-aspartate

- Some examples of recommended non-drug management for mild to moderate dementia includes; social support, increasing assistance with day-to-day activities, information and education, carer support groups, community dementia teams, home nursing and personal care, community services, befriending services, and day centres.[22]

Where will lecanemab be used in the treatment pathway for Alzheimer's disease?
Subject to MHRA approval, lecanemab will be offered to patients with early Alzheimer's disease (either MCI due to Alzheimer's disease or mild dementia due to Alzheimer's disease), as shown in the figure below.



AD: Alzheimer's disease

There are no drug treatments for patients with MCI due to Alzheimer's disease. The current drug treatments for mild dementia due to Alzheimer's disease only provide temporary relief of the symptoms of the disease, which continues to worsen over time. The current symptomatic drug treatments do not treat the underlying cause of Alzheimer's disease nor slows the progression of the disease. In contrast, lecanemab is a disease modifying treatment which aims to slow progression of Alzheimer's disease (subject to MHRA approval).

It is expected that symptomatic drug treatments (AChE inhibitors and memantine) will continue to be offered to patients treated with lecanemab as required. Therefore, the approval of lecanemab will not impact patient's access to these therapies.

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.

The What Matters Most study[23]

The aim of this study was to quantify the importance of symptoms, impacts, and outcomes of Alzheimer's disease to:

- individuals at risk for Alzheimer's disease or patients with Alzheimer's disease
- care partners (or carers) of patients with Alzheimer's disease

What did the study ask?

A web-based survey was used to collect responses. Respondents rated the importance of 42 symptoms, impacts, and outcomes on a scale ranging from 1 ("not at all important") to 5 ("extremely important").

What was learned from the study?

The 'What Matters Most' patient and care partner survey concluded that maintaining independence, overall physical and mental health, emotional well-being, and safety were most important to the respondents.

U.S. FDA Committee Meeting - June 2023[24]

As part of the regulatory approval process for lecanemab in the United States, the Food and Drug Administration (FDA) held a public committee meeting on 9th June 2023.[24] During this virtual meeting, some patients with early Alzheimer's disease and their carers who took part in the Clarity AD clinical study of lecanemab shared their experience of Alzheimer's disease.

Alzheimer's disease from the patient's perspective
One patient described how long it took to get a diagnosis. "*It was a gruelling, frustrating eight years to get a proper and correct diagnosis. The same diagnosis as two of my Aunts. I knew what would be in store for me and my family and their experiences; that it was going to be difficult and something had to change. The path was to enroll in a clinical trial."* – Speaker #22 (timepoint 5h36m)

Following a diagnosis, patients are often no longer able to work. "*Because of my [Alzheimer's disease] diagnosis, I was forced to retire at the age of 63. I walked out of my office for the very last time, and the world I knew and loved had ended. It was a sudden end to my old life, and I had to find a new one and a purpose to pursue in that new life, because everything I had planned on my life being was gone*" - Speaker #17 (timepoint 5h03m)

One patient described her symptoms. "*I started having memory problems on a daily basis, like getting to the kitchen and not remembering why I was there. Forgetting names and events and how to use the computer. My husband was greatly affected by this and had to make adjustments, taking care of details that I used to be in charge at home like cooking, remembering my appointments, and dealing with my emotional frustrations*." – Speaker #19 (timepoint 5h26m)

Another patient expressed what was most important to her future, living with Alzheimer's disease. "*My diagnosis helped me to reprioritise my life and made clear what was most meaningful. Remaining independent for as long as possible. Having more time to travel. Meeting my future grandchildren. Singing in my church choir*". – Speaker #22 (timepoint 5h36m)

Alzheimer's disease from the carer's perspective
One carer described how she felt after learning of her loved one's diagnosis. *"My immediate reaction was fear, confusion and hopelessness for our future."* - Speaker #11 (5h04m)

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

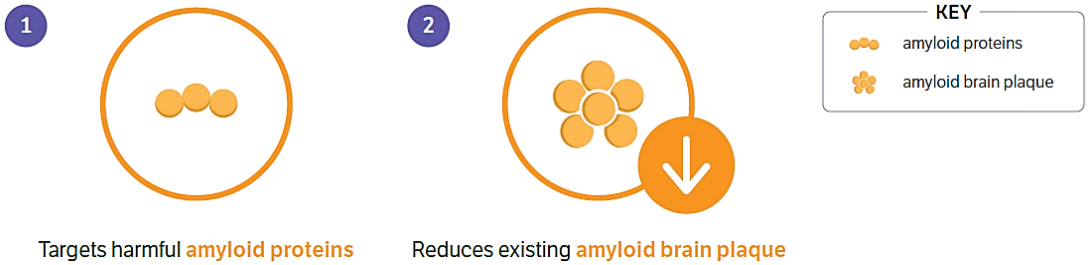
Where possible, please describe how you feel the medicine is innovative or novel, and how this might be important to patients and their communities.

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.

What is lecanemab?
Lecanemab is a **monoclonal antibody**. Monoclonal antibodies act like natural substances made in the body and work by binding to a target protein to reduce the harmful effect of

that protein. Lecanemab binds to a protein called amyloid beta, which is involved in Alzheimer's disease.

How does lecanemab work?



In Alzheimer's disease, there is too much amyloid beta protein which continuously builds up and eventually clumps together to form plaques in the brain. Lecanemab works by targeting harmful amyloid proteins and reducing existing amyloid brain plaques in the early stages of Alzheimer's disease. Consequently, lecanemab could slow the progression of the disease meaning patients could remain in the milder, more independent stages of Alzheimer's disease for longer.

3b) Combinations with other medicines

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

- Yes / No

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.

Lecanemab is not a combination treatment. However, other medications may be taken alongside lecanemab under the supervision of a prescribing doctor.

In the Clarity AD study (see section 3d), over half of patients were taking medication for symptoms of Alzheimer's disease alongside lecanemab. Almost all patients were taking regular medication for conditions not relating to Alzheimer's disease.

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 lecanemab will be given and how long it takes?[25]

- Lecanemab will be given under the supervision of a healthcare professional as a 'drip' (a needle placed in a vein) also called an intravenous (IV) infusion.
- Each infusion will last about 1 hour, but patients may be at the clinic for longer.
- Patients will be given a recommended dose of 10 milligrams per kilogram of body weight, for example a patient weighing 70 kilograms will be given 700 milligrams of lecanemab.
- Infusions are given once every 2 weeks. If an infusion is missed, the next dose will be given as soon as possible.

How might the dosing regimen of lecanemeb affect patients and carers?[25]

- Patients will need to commit to visit the clinic for their infusions every 2 weeks.
- Carers may need to help coordinate (and attend) appointments to make it easier for patients to stay on track.
- As part of the routine follow-up of being on treatment, patients will have additional tests or MRI scans as instructed by their doctor (described further in section 3g).
- Doctors may recommend pausing or stopping stop treatment depending on clinical test results.

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.

The drug manufacturer (Eisai) conducted clinical trials to test the safety and to see how lecanemab works in patients with early Alzheimer's disease who had confirmed increased levels of amyloid proteins. In the clinical trials, lecanemab was compared to a placebo - a placebo is a treatment that appears real, but it has no drug effect.

The information in the table below was taken from the Clinicaltrials.gov website (www.clinicaltrials.gov) on 10 November 2023, and shows lecanemab trials in patients with early Alzheimer's disease (which is MCI or mild dementia due to Alzheimer's disease).

Study name	Phase	Location	Patient group	Number enrolled	Treatments studied	Expected completion date
NCT01767311, BAN2401-G000-201	II	Canada, France, Germany, Italy, Japan, Republic of Korea, Netherlands, Spain, Sweden, United Kingdom, United States.	Early Alzheimer's disease	856	Various doses of lecanemab and placebo	18-month core study is completed. Open-label extension phase* is ongoing, expected completion in 2025.
NCT03887455, **Clarity AD**	III	Australia, Canada, China, France, Germany, Italy, Japan, Republic of Korea, Russian Federation, Singapore, Spain, Sweden, United Kingdom, United States.	Early Alzheimer's disease	1906	Lecanemab and placebo	18-month core study is completed. Open-label extension phase* is ongoing, expected completion in 2027.

* Subject to eligibility, patients who completed the core study had the option to continue in the open-label extension part of the clinical trial. This means that **all patients** are treated with lecanemab (10mg/kg every 2 weeks), including those patients who were on placebo treatment before in the core study.

The pending marketing authorisation from the MHRA is based on the results from the phase III **Clarity AD study**. The key publication of the study by van Dyck et al. (2023)[26] can be found here: https://www.nejm.org/doi/full/10.1056/NEJMoa2212948

Who was included in the Clarity AD study?

- 1,795 men and women were treated with lecanemab or placebo.
- Ages 50 to 90.
- With MCI or mild dementia due to Alzheimer's disease.
- With confirmation of increased levels of amyloid proteins by PET scan or CSF test.
- From different ethnic and racial backgrounds.

Who was excluded from the Clarity AD study?

Key exclusion criteria were:

- Any neurological condition that could contribute to cognitive impairment above and beyond that caused by the patient's AD.
- History of mini stroke, stroke or seizures within the last 12 months.
- Any psychiatric diagnosis or symptoms, (eg, hallucinations, major depression, or delusions).
- Any clinically significant lesions or pathology of the brain that could indicate a dementia diagnosis other than AD.
- Any immunological disease which is not adequately controlled, or which requires specific medication.
- Any other medical conditions (for example, cardiac, respiratory, gastrointestinal, renal disease) which are not stable and adequately controlled.

What assessments were done in the Clarity AD study?

After confirmation of eligibility, patients attended a baseline visit (Month 0) with their study partners (primary caregiver) and were randomly assigned to the lecanemab group or placebo group. The study was double blinded which means that neither the patient/study partner nor the study investigator/team knew what treatment the patient was assigned to. There were regular study visits thereafter until Month 18. During these study visits the patient had clinical assessments and scans to monitor safety and physical signs of disease progression, following the protocol schedule of assessments.

- Patients completed validated scales or questionnaires to measure their cognition, function and quality of life.
- Study partners also completed a quality-of-life questionnaire on behalf of the patient as a proxy, as well as a questionnaire to measure their own quality of life. Additionally, study partners were interviewed to assess caregiver burden (i.e. to evaluate the stresses experienced by carers of patients with Alzheimer's disease).

What were the key outcome measures in the Clarity AD study?

The primary outcome measure (also called an 'endpoint') was the change in the score on the Clinical Dementia Rating (CDR)-Sum of Boxes (SB) scale, comparing the baseline score when patients started treatment to the score at 18 months.

- The CDR-SB is a validated scale that is commonly used to assess Alzheimer's disease in clinical trials.
- CDR-SB broadly measures 6 areas of cognition and function that patients and caregivers identify as important to represent 'a sense of self' and the ability to function independently. These are:
    - Memory
    - Orientation (e.g. perception of time)
    - Judgement, problem solving
    - Community affairs (e.g. job, shopping, social functions outside of home)
    - Home & hobbies
    - Personal care

The following key secondary outcome measures compared the change over time from the baseline score (i.e. when patients start treatment) to the score at 18 months:

- Amyloid PET scan to measure the amount of amyloid plaques in the brain
- ADAS-Cog14, a scale measuring cognition (i.e. how a person thinks or feels)
- ADCOMS, a scale measuring cognition and function
- ADCS MCI-ADL, a scale measuring the ability to perform activities of daily living

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.

Clarity AD study results

The study was divided equally into 2 groups. One group took lecanemab (898 people) and the other placebo group did not take lecanemab (897 people).

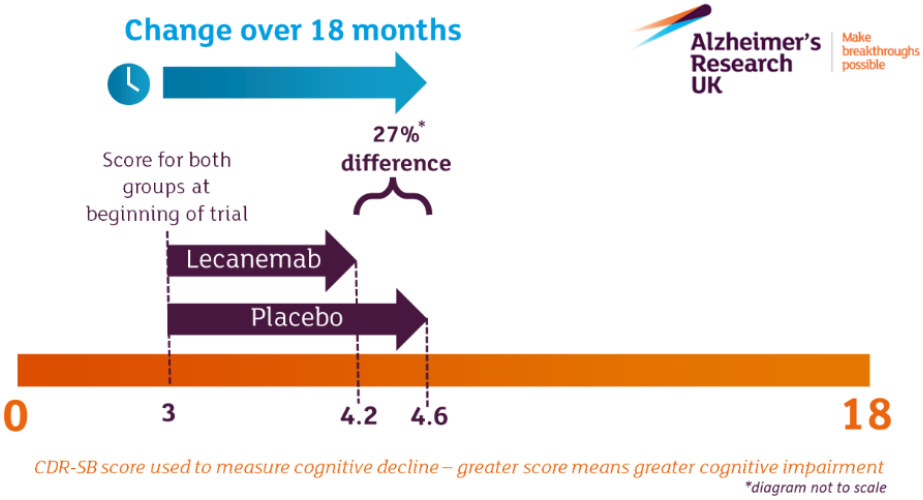
The efficacy of lecanemab was measured according to how well it could:

1. Reduce the impact of disease on cognition and function of patients
2. Reduce the amount of amyloid plaques in the brain
3. Delay progression to later stages of disease

This is described further below.

1. Impact of disease on cognition and function of patients was measured using various scales, these were: CDR-SB, ADAS-Cog14, ADCOMS and ADCS MCI-ADL.

- **Patients treated with lecanemab showed less clinical decline in their cognition and function compared to patients on placebo treatment (i.e. less worsening of disease symptoms) at 18 months.[26]**
- There was a 27% less decline in the CDR-SB score for the lecanemab group compared to placebo, which was highly statistically significant.



Ref: Alzheimer's Research UK. New Alzheimer's treatment, lecanemab, makes the headlines: what's next?[27]

2. Reduce the amount of amyloid plaques in the brain

- **Patients treated with lecanemab showed a sharp (highly statistically significant) reduction in amyloid levels in their brain compared to patients on placebo treatment at 18 months.[26, 27]**

3. Delay progression to later stages of disease
    - **Patients treated with lecanemab progressed more slowly to the next stage of Alzheimer's disease compared to patients on placebo treatment at 18 months, meaning patients remain in more independent stages of the disease for longer (results were highly statistically significant).[26]**

The main conclusion about efficacy from the publication of the Clarity AD study by van Dyck et al (2023) was as follows:

In adults with early Alzheimer's disease (mild cognitive impairment or mild dementia due to Alzheimer's disease), lecanemab was associated with less disease progression than placebo over 18 months. This could allow patients to maintain their memory, thinking skills, and complete daily activities for longer. However, more research is needed to confirm these results beyond the 18 months that patients have been followed up for in the Clarity AD study so far.

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.

In the Clarity AD study, the health-related quality of life of patients was measured using the EQ-5D-5L instrument which covers 5 dimensions of health (mobility, self-care, usual activities, pain or discomfort, and anxiety or depression) with 5 levels of severity in each level.

- **Patients treated with lecanemab showed less decline in their EQ-5D-5L quality of life scores compared to patients on placebo treatment at 18 months (results were highly statistically significant).**

To assess the caregiver burden in the patient's study partner, the Zarit Burden Interview was used.

- **Study partners (carers) of patients treated with lecanemab showed less decline in their carer burden scores compared to patients on placebo treatment at 18 months (results were highly statistically significant).**
- This effect was consistent across all 22 domains of the Zarit Burden Interview, favouring lecanemab. This shows that lecanemab treatment, addresses common caregiver concerns, such as not having enough time, money, privacy, or feeling as if one's relationships and social life have suffered.
- Less decline suggests that lecanemab treatment can alleviate a portion of the caregiving burden for carers of patients with AD. This can lead to improved mental and emotional health of carers, reduced caregiver burnout, and enhanced family dynamics.[28]

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.

What is the most important information patients should know about lecanemab?
Like all medicines, lecanemab can cause side effects, although not everybody gets them. The most common side effects in the Clarity AD study[26] (in more than 10% of patients in either the lecanemab or placebo treatment groups) were;

Side effect	**% of patients with this side effect**	
	Lecanemab	**Placebo**
Infusion-related reaction	26%	7%
ARIA with microhaemorrhages or hemosiderin deposits	14%	8%
ARIA-E	13%	2%
Headache	11%	8%
Fall	10%	10%

Source: Adapted from Table 3 of the van Dyck et al. (2023) publication.[26]
ARIA: amyloid-related imaging abnormalities; ARIA-E: ARIA-oedema/effusion

Infusion-related reactions are a possible side effect of lecanemab. These include fever, flu-like symptoms (chills, body aches, feeling shaky, and joint pain), nausea, vomiting, dizziness or light-headedness, changes in heart rate or feeling like your chest is pounding, changes in blood pressure, and difficulty breathing or shortness of breath.

Infusion-related reactions are mostly mild to moderate in severity. Infusion-related reactions usually occurred during the first 2 treatments and typically resolved within 24 hours.[29] If a patient has an infusion-related reaction, the doctor may give preventative medicines before the next lecanemab infusions to decrease the chance of having an infusion-related reaction. These medicines may include antihistamines, anti-inflammatory medicines, or steroids.

Amyloid related imaging abnormalities or "ARIA" are a possible serious side effect of lecanemab. ARIA is a side effect that does not usually cause symptoms, but serious symptoms can occur. There are two types of ARIA (ARIA-E and ARIA-H). ARIA-E is most commonly seen as temporary fluid in one or more regions of the brain, visible on a MRI brain scan. Some people may also have small spots of bleeding in or on the surface of the brain (ARIA-H), and infrequently, larger areas of bleeding in the brain can occur. Most people with ARIA do not experience symptoms, however some people may have symptoms, such as: headache, confusion, dizziness, blurry vision, nausea (feeling sick), vomiting (being sick), or seizures (fits). Most symptoms go away within 4 months.[29]

If ARIA is detected on an MRI scan, there are different lecenemab treatment recommendations for patients dependent on (1) the severity of ARIA seen on MRI, and (2) the severity of symptoms experienced by the patient. The doctor may advise the patient to 'continue treatment as usual', or 'suspend treatment', or 'stop treatment'.[29]

Overall, lecanemab was generally well tolerated and about 7% of patients stopped taking treatment because of side effects.[26]

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 lecanemab for early Alzheimer's disease patients, carers and their communities are:

- **Slower decline of patient's cognition and function,** which means patients can maintain their independence for longer.
- **Sharp reduction of patient's amyloid beta levels in the brain**, which reduces existing amyloid brain plaques.[27]
- **Slower progression of patients to later stages of Alzheimer's disease,** which can lead to a better quality of life for patients and carers, and delays carer burden.

The Clarity AD study results indicate that lecanemab has the potential to delay the decline in patient's activities of daily living and quality of life. This could allow patients to maintain their functional capacities and live independently for longer in the milder stages of the condition; prolonging the time spent with higher quality of life for both the patient and their caregiver.

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

The key disadvantages of lecanemab for early Alzheimer's disease patients, carers and their communities are:

- **Possible infusion-related reactions**; these are easily managed and resolve quickly. If they do occur, preventative medications can be given before the next infusion.
- **Possible ARIA side effects**; patients will be closely monitored for ARIA events when they start lecanemab. If an event does occur, they will be followed up by their doctor (see section 3g).

It is important to note that not all patients will experience side effects.

3j) 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.

How the company's model reflects Alzheimer's disease

A health economic model called a 'Markov model' was used to simulate a patient's progression from MCI due to Alzheimer's disease (AD), to mild AD, to moderate AD, to severe AD, to death.

- Disease progression in the model was defined by CDR-SB scores which was the primary outcome measure in the Clarity AD study.
- Two groups of patients were modelled, a 'lecanemab treatment group' and a 'standard of care treatment group'.
- The model compared the differences between the two treatments in terms of **quality-adjusted life years (QALYs)** and **costs**.
    - A QALY is a measure of a person's length of life, adjusted to reflect the quality of life in numerical terms.
- The model simulates the 18-month Clarity AD study period and beyond through the subsequent stages of Alzheimer's disease until the patient's death.

Modelling improvements in survival and quality of life between lecanemab and standard of care

- The model estimated the total time patients spent in each of the four stages of Alzheimer's disease over their lifetime.
- In the Clarity AD study, patients who were treated with lecanemab spent more time in early AD (i.e. MCI due to AD and mild AD) and less time in moderate and severe AD, compared to those on standard of care treatment.
- Prolonging the time spent in milder stages of Alzheimers disease generated benefits for lecanemab compared to standard of care such as:
    - Maintaining a higher quality of life for both the patient and their caregiver in the milder stages.
    - A survival benefit due to the delayed time to more severe stages of AD which is associated with higher mortality
    - Increased time spent in community care (in own home) and reduced time spent in institutional care
- This meant that lecanemab patients had more QALYs overall compared to standard of care.

Modelling differences in costs between lecanemab and standard of care

- The model considered different costs associated with patients being on treatment paid for by the NHS and Personal Social Services. These include the cost of lecanemab, administering the infusions, diagnostic testing (to confirm levels of amyloid beta), monitoring, and management of side effects.
- Costs associated with standard of care treatment included the cost of symptomatic drugs and management of side effects.
- The standard of care treatments (see section 2c for details) are low cost and are tablets so they have no administration costs. This meant that treatment with lecanemab generated more costs paid for by the NHS and Personal Social Services than current standard of care.

Uncertainty

Data from the Clarity AD study were used in the model where possible. Other data inputs were obtained by extensively searching relevant publications on Alzheimer's disease in a systematic way. However, not all the data inputs needed for the model were found and assumptions had to be made instead. Some key assumptions were:

- The cost of administering lecanemab was based on the NHS cost of administering a chemotherapy as a proxy, because there is currently no existing NHS cost for this.
- The effect of lecanemab beyond the 18-month timeframe of the Clarity AD study. It is expected that the ongoing Clarity AD open-label extension (OLE) study that followed patients for longer than 18-months will provide further insights.

Interpreting the cost effectiveness results

- The model estimated that lecanemab generated more QALYs at higher average costs compared to standard of care.
- Lecanemab is also expected to generate benefits that cannot be captured in the model, such as the value of hope to patients and their carers that such a treatment can provide.
- This model does not fully capture all aspects of the carer's quality of life, such as:
    - The substantial financial impacts to families and society resulting from caregivers having less time to work due to the time spent providing unpaid care for their loved one.[30]
    - The impact of caregivers being absent from work due to health problems such as stress and depression.[23]

Overall, lecanemab could be considered a cost-effective use of NHS resources to treat patients with early Alzheimer's disease, as patients stay in milder stages of disease for longer which is beneficial for them and their caregiver.

3k) 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)

In contrast to existing Alzheimer's disease treatments that only treat symptoms, lecanemab is a disease modifying treatment that has been shown to slow down the progression of early Alzheimer's disease in the 18-month Clarity AD study. This could allow patients to maintain their functional capacities and live independently for longer in the milder stages of the condition; prolonging time spent with a higher quality of life for the patient and a lower mortality risk. In addition, lecanemab has the potential to reduce the burden of caregiving on families.

3l) 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 known equality issues relating to the use of lecanemab in patients with early Alzheimer's disease.

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.
UK patient groups and charities: • Alzheimer's Research UK https://www.alzheimersresearchuk.org/ • Alzheimer's Society https://www.alzheimers.org.uk/ • Brace Dementia Research https://www.alzheimers-brace.org/ • Dementia UK https://www.dementiauk.org Further information about Alzheimer's disease: • Help and support for people with Dementia – NHS https://www.nhs.uk/conditions/dementia/care-and-support/help-and-support/#:~:text=Alzheimer%27s%20Society%20runs%20the%20Dementia,life%20for%20people%20with%20dementia. • Alzheimer's Disease – NHS. https://www.nhs.uk/conditions/alzheimers-disease/ • Alzheimer's Society. Alzheimer's Disease https://www.alzheimers.org.uk/about-dementia/types-dementia/alzheimers-disease • Alzheimer's Society. What is Alzheimer's disease? You Tube https://www.youtube.com/watch?v=wfLP8fFrOp0 • Alzheimer's Research UK. What is Alzheimer's disease? https://www.alzheimersresearchuk.org/dementia-information/types-of-dementia/alzheimers-disease/ • Age UK. Dementia symptoms and types of dementia. https://www.ageuk.org.uk/information-advice/health-wellbeing/conditions-illnesses/dementia/understanding-dementia/ • Alzheimer's Disease International. Alzheimer's disease. https://www.alzint.org/about/dementia-facts-figures/types-of-dementia/alzheimers-disease/ • Alzheimer Europe. Alzheimer's dementia. https://www.alzheimer-europe.org/dementia/alzheimers-disease • BRACE Dementia research. Alzheimer's Disease https://www.alzheimers-brace.org/alzheimers-disease-ad/ • Dementia UK. What is Alzheimer's Disease https://www.dementiauk.org/information-and-support/types-of-dementia/alzheimers-disease/ • World Health Organisation. Dementia. https://www.who.int/news-room/fact-sheets/detail/dementia • BUPA UK. Alzheimer's disease Health Information. https://www.bupa.co.uk/health-information/dementia/alzheimers-disease • NHS inform Alzheimer's disease. https://www.nhsinform.scot/illnesses-and-conditions/brain-nerves-and-spinal-cord/alzheimers-disease/ Further information about lecanemab: • Alzheimer's Society. Lecanemab: A new drug for early-stage Alzheimer's disease. https://www.alzheimers.org.uk/blog/lecanemab-new-drug-early-stage-alzheimers-disease • Alzheimer's Research UK. New Alzheimer's treatment, lecanemab, makes the headlines: what's next? https://www.alzheimersresearchuk.org/blog/new-alzheimers-treatment-lecanemab-makes-the-headlines-whats-next/ • Alzheimer's Disease International https://www.alzint.org/?s=lecanemab

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
- EUPATI guidance on patient involvement in NICE: https://www.eupati.eu/guidance-patient-involvement/
- EFPIA – Working together with patient groups: https://www.efpia.eu/media/288492/working-together-with-patient-groups-23102017.pdf
- National Health Council Value Initiative. https://nationalhealthcouncil.org/issue/value/
- INAHTA: http://www.inahta.org/
- European Observatory on Health Systems and Policies. Health technology assessment - an introduction to objectives, role of evidence, and structure in Europe: http://www.inahta.org/wp-content/themes/inahta/img/AboutHTA_Policy_brief_on_HTA_Introduction_to_Objectives_Role_of_Evidence_Structure_in_Europe.pdf

4b) Glossary of terms

Activities of daily living include eating, bathing, grooming, dressing and going to the toilet. People with dementia may need help to perform these tasks.

ADAS-Cog14 stands for Alzheimer's Disease Assessment Scale–Cognitive Subscale 14-task version. It is a scale measuring cognition (i.e. how a person thinks or feels).

ADCOMS stands for Alzheimer's disease composite score. It is a scale measuring cognition and function.

ADCS MCI-ADL stands for the Alzheimer's Disease Cooperative Study-Activities of Daily Living Scale for use in Mild Cognitive Impairment. It is a scale measuring the ability to perform activities of daily living.

Amyloid beta is a normal protein in the human brain. In Alzheimer's disease, clumps of amyloid beta protein form plaques in the brain.

Amyloid PET is a positron emission tomography (PET) scan that specifically detects and measures the amount of amyloid protein in the brain.

ARIA stands for amyloid-related imaging abnormalities, which are abnormal differences seen in magnetic resonance imaging (MRI) scans of the brain in patients with Alzheimer's disease. There are two types of ARIA: ARIA-E and ARIA-H.

ARIA-E stands for ARIA-oedema/effusion. ARIA-E refers to accumulation of fluid (oedema) in the brain. Effusion means too much fluid or outpouring of fluid.

ARIA-H stands for ARIA-hemosiderin/haemorrhage. ARIA-H refers to microbleeds (or microhaemorrhages) on the brain, which is often accompanied with the build-up of hemosiderin (a form of iron that is usually found inside red blood cells).

Biomarker is a characteristic of the body that can be measured. Some biomarkers can be used to detect or confirm the presence of a disease or condition of interest.

Clinical study or clinical trial (used interchangeably), a study or trial to determine whether a treatment is safe and effective. It is carried out with a sample of patients, usually after laboratory studies and studies with healthy volunteers have been conducted. The trial is set up to answer 1 or more questions, for example, does the treatment have any adverse side effects and, if so, how serious are they?[31]

Caregiver or carer (used interchangeably), anyone who provides care to a person with Alzheimer's disease or dementia. Caregivers can be family members or friends, or paid professional caregivers. Caregivers may provide full- or part-time help to the person with Alzheimer's.

CDR-SB stands for Clinical Dementia Rating-Sum of Boxes scale. It is a scale that is commonly used to assess Alzheimer's disease in clinical trials.

Cognition is a term for the mental processes that take place in the brain, including thinking, attention, language, learning, memory and perception.[32]

Dementia is not a specific disease. It is an overall term that describes a wide range of symptoms associated with a decline in memory or other thinking skills severe enough to reduce a person's ability to perform everyday activities. Alzheimer's disease is the most common type of dementia.
EQ-5D-5L stands for EuroQol-5D with 5 levels. It is a standardised 5-dimensional instrument used to measure health outcomes.[31]
Function is a term for the ability to perform tasks such as eating, bathing, grooming, dressing, going to the toilet and walking without help.
MCI stands for mild cognitive impairment. MCI describes memory and thinking problems that are mild but still noticeable.
MHRA stands for the Medicines and Healthcare products Regulatory Agency. MHRA regulates medicines, medical devices and blood components for transfusion in the UK.
MRI scan stands for magnetic resonance imaging scan. It is a type of scan that uses strong magnetic fields and radio waves to produce detailed images of the soft tissues of the body.
Quality of life refers to the standard of health, comfort, and happiness experienced by an individual or group.
QALY stands for quality-adjusted life year. It is a measure of the state of health of a person or group. The length of life remaining is adjusted to reflect the quality of life in numerical terms. One QALY is equal to 1 year of life in perfect health.[31]
Stages is a framework for the progression of Alzheimer's disease.
Standard of care is a guideline for appropriate treatment of a condition or disease, and is whatever most physicians agree is the best way to treat that condition or disease.

4c) References

Please provide a list of all references in the Vancouver style, numbered and ordered strictly in accordance with their numbering in the text:

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

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

Clarification questions

January 2024

File name	Version	Contains confidential information	Date
ID4043_Lecanemab_EAG clarification letter_29Jan24_CIC V3.0 FINAL_REDACTED	Final	Yes	4th June 2024

Section A: Clarification on effectiveness data

Literature searches

A 1. Both the clinical SLR and economic searches report a single search strategy for both Medline and Embase searches via Embase.com. Please confirm if this is a single search of the Embase database conducted on the understanding that it now contains all records from Medline.

Company response: Yes, a single search was conducted to cover both Medline and Embase searches via the Embase.com interface due to overlapping coverage between the two databases. However, PubMed was also searched separately to identify any in-process or Ahead of Print citations.

A 2. Please confirm whether any additional searches, other than those reported in Appendix D section D.1, were conducted to retrieve information regarding adverse events (AEs) for lecanemab and, if so, provide full details including date, resource names and search strategies used.

Company response: The search of clinical evidence (including adverse events) included core biomedical databases, i.e., Embase, PubMed, and Cochrane Library. This was supplemented by a search of relevant conference proceedings to identify abstracts/posters that have not yet been published as a manuscript. No additional searches were conducted to identify adverse events for lecanemab or any other treatment of interest, as these were sourced from Clarity AD, the pivotal study supporting the marketing authorisation of lecanemab.

A 3. Both the clinical (appendix D) and Costs (Appendix G) sections mention conference proceedings other than those retrieved by Embase, a list of named conference is provided but no information as to search terms or hits per resource. Please provide full details for each section including date searched.

Company response: Please see Table 1 for a summary of conference search details for the clinical and cost SLRs, including the number of citations manually screened on each website. Conference proceedings were hand-searched between October 16th and October 20th 2023 on the websites detailed in Table 1. The following keywords were screened on each website: “mild cognitive”, “cognitive

impairment", "MCI", "dementia", "mild dementia", "Alzheimer's", "lecanemab", "BAN 2401, "donepezil", "galantamine", "rivastigmine", "cognitive rehabilitation", "cognitive stimulation", "reminiscence". The same keywords were searched in all conference proceedings for all SLRs.

Abstracts for Annual Congress of the European Academy of Neurology (EAN) and American Academy of Neurology (AAN) were already indexed and available within the conference coverage of the Embase data.

Table 1: Conference search details for clinical and cost SLRs

Conference	Years searched via Embase.com	Years searched via conference websites	Website	Number of citations screened
AAIC – Annual Alzheimer's Association International Conference	(-)	2020, 2021, 2022, 2023	2020-23: https://aaic.alz.org/abstracts/abstracts-archive.asp	The complete set of supplements/volumes (including all abstracts) was manually screened. 2020: 3,494 citations 2021: 3,887 citations 2022: 2,967 citations 2023: 5,414 citations
EAN – Annual Congress of the European Academy of Neurology	2020 (indexed)*	2021, 2022, 2023	2021: 1) https://www.ean.org/fileadmin/user_upload/ean/congress-2021/EAN2021AbstractBook.pdf 2) https://www.ean.org/fileadmin/user_upload/ean/congress-2021/EAN2021LateBreakingAbstracts.pdf 2022: https://www.ean.org/fileadmin/user_upload/ean/congress-2022/EAN2022AbstractBook.pdf 2023: https://www.ean.org/fileadmin/user_upload/ean/congress-2023/EAN2023AbstractBook.pdf	All abstracts included in each PDF were manually screened

ANA – American Neurological Association	(-)	2020, 2021, 2022, 2023	2020: https://onlinelibrary.wiley.com/doi/epdf/10.1002/ana.25865 2021: https://onlinelibrary.wiley.com/doi/abs/10.1002/ana.26180 2022: https://onlinelibrary.wiley.com/doi/epdf/10.1002/ana.26484 2023: https://onlinelibrary.wiley.com/doi/epdf/10.1002/ana.26747	All abstracts available on each website were manually screened
AAN – American Academy of Neurology	2020, 2021, 2022, 2023 (indexed)	(-)	(-)	(-)
ADI – International Conference of Alzheimer's Disease International	(-)	2020, 2022 (biennial)	2020: https://www.alzint.org/u/ADI-2020-Abstract-Book.pdf 2022: https://adiconference.org/files/general/ADI-2022-Abstract-Book.pdf	All abstracts included in each PDF were manually screened

CTAD – Clinical Trials on Alzheimer's Disease	(-)	2020, 2021, 2022. (2023 was not yet published per our review timeframe)	2020: https://www.ctad-alzheimer.com/files/files/CTAD%202020%20Abstracts%20final.pdf 2021: 1) https://www.ctad-alzheimer.com/files/files/CTAD21%20Oral%20communications.pdf 2) https://www.ctad-alzheimer.com/files/files/CTAD21%20Posters.pdf 2022: 1) https://link.springer.com/article/10.14283/jpad.2022.96 2) https://link.springer.com/article/10.14283/jpad.2022.97	All abstracts (including those for posters and oral presentations) available on each website were manually screened

AD/PD – Alzheimer's & Parkinson's Diseases	(-)	2021, 2022, 2023 (not available for 2020 period)	2021: https://cslide.ctimeetingtech.com/adpd21/attendee/eposter 2022: Conference Calendar - 16th International Conference on Alzheimer's and Parkinson's Diseases: Mechanisms, Clinical Strategies and promising Treatments of Neurodegenerative Diseases (ctimeetingtech.com) 2023: https://cslide.ctimeetingtech.com/global_storage/media/content/adpd23/ADPD23_-_Posters_for_website_Mar_29.pdf	2021: 676 posters + oral presentations 2022: 633 + oral presentations 2023: All citations (AD-specific) in the PDF were manually screened.
ISPOR – International Society for Pharmacoeconomics and Outcomes Research	(-)	2020, 2021, 2022, 2023	https://www.ispor.org/heor-resources/presentations-database/search	Keywords searched: Mild cognitive impairment: 63 MCI: 45 Dementia: 261 Alzheimer: 33

*The conference abstracts for the years specified were already indexed and available within the conference coverage of Embase database (second column). The manual searching of conference proceedings was only done for those that were not indexed within Embase. The details of specific years are mentioned in the third column.
Abbreviations: AAIC – Alzheimer's Association International Conference; AAN – American Academy of Neurology; AD/PD – Alzheimer's & Parkinson's Diseases; ADI – Alzheimer's Disease International; ANA – American Neurological Association; CTAD – Clinical Trials on Alzheimer's Disease; EAN – European Academy of Neurology; ISPOR – International Society for Pharmacoeconomics and Outcomes Research.

A 4. Please can you confirm that Wiley is the host used for the Cochrane Library searches.

Company response: Yes, the Wiley online interface was used to search the Cochrane Library.

Decision problem

A 5. PRIORITY QUESTION The company submission (CS) (Table 1, pg 10) states that the comparator in the decision problem addressed by the CS was non-pharmacological management, for the MCI due to AD population. The CS does not include any data about the comparative effects of lecanemab vs. non-pharmacological management in the MCI due to AD population. This is because the key study (Clarity AD) was conducted in a mixed population (MCI due to AD and mild dementia due to AD) and over half of the patients in the study were receiving other pharmacological interventions for AD (AChEI and/or memantine). Some subgroup analyses were provided, for clinical subgroup (MCI due to AD and mild dementia due to AD) and for use of symptomatic AD medication at baseline (yes and no).

Please provide subgroup analyses, for all reported outcomes (CDR-SB, ADAS-Cog14, ADCOMS and ADCS MCI-ADL), for participants with MCI due to AD, who did <u>not</u> receive symptomatic AD medication (AChEI or memantine) during the study.

Company response: The results of subgroup analyses for the MCI due to AD population who did not receive symptomatic AD medication at baseline in Clarity AD for CDR-SB, ADAS-Cog14, ADCOMS and ADCS MCI-ADL are presented in Table 2, Table 3, Table 4, and Table 5, respectively. These results in subgroups need to be interpreted with caution due to the small sample size and the slower clinical progression in MCI relative to mild AD. Within the MCI stratum (60% of CLARITY AD study population), results favoured lecanemab, which were consistent with the overall results: clinical and functional outcomes, quality of life measures, and biomarkers demonstrating impact on the underlying biology. A small proportion of these patients (approximately [redacted], [redacted] in the lecanemab arm and [redacted] in the placebo arm) began treatment with symptomatic AD medication during the 18-month study. It

was assumed this would not have a material impact on the results of the subgroup analyses, therefore further analyses to exclude these patients from the subgroup were not conducted.

It should be noted that ADCOMS is a composite endpoint comprised of the CDR (all 6 items), the ADAS-Cog14 (4 items), and the MMSE (2 items), it was used to facilitate the response adaptive component of the Bayesian design for the Study 201 Core study and was included in Clarity AD to demonstrate reproducibility of results.

Table 2: Statistical analysis of change from baseline in CDR-SB at 18 months - MMRM, Clarity AD Core study, MCI due to AD not treated with symptomatic AD medication at baseline subgroup

Statistic	Lecanemab (n=[redacted])	Placebo (n=[redacted])
Number of patients included in the MMRM	[redacted]	[redacted]
Number of subjects at 18-month visit (week 79)	[redacted]	[redacted]
Mean CDR-SB at baseline (SD)	[redacted]	[redacted]
Adjusted mean change from baseline at 18 months (SE)	[redacted]	[redacted]
Adjusted mean difference (lecanemab – placebo)	[redacted]	
95% confidence interval (CI) for differences	[redacted]	
p-value	[redacted]	
% Difference vs. placebo	[redacted]	

Abbreviations: AD – Alzheimer's disease; CDR-SB – Clinical Dementia Rating - Sum of Boxes; CI – Confidence interval; MCI – Mild cognitive impairment; MMRM – mixed model for repeated measures; SE – Standard error.
Source: Eisai data on file: Biostatistics analyses for AMNOG

Table 3: Statistical analysis of change from baseline in ADAS-Cog14 at 18 months – MMRM, Clarity AD Core study, MCI due to AD without symptomatic AD medication at baseline subgroup

Statistic	Lecanemab (n=[redacted])	Placebo (n=[redacted])
Number of patients included in the MMRM	[redacted]	[redacted]
Number of subjects at 18-month visit (week 79)	[redacted]	[redacted]
Mean ADAS-Cog14 at baseline (SD)	[redacted]	[redacted]
Adjusted mean change from baseline at 18 months (SE)	[redacted]	[redacted]
Adjusted mean difference (lecanemab – placebo)	[redacted]	
95% confidence interval (CI) for differences	[redacted]	
p-value	[redacted]	
% Difference vs. placebo	[redacted]	

Abbreviations: ADAS-Cog14 – Alzheimer's Disease Assessment Scale - Cognitive subscale 14-item version; AD – Alzheimer's disease; CI – Confidence interval; MCI – Mild cognitive impairment; MMRM – mixed model for repeated measures; SE – Standard error.
N shows the number of subjects at each visit.

Source: Eisai data on file: Biostatistics analyses for AMNOG

Table 4 Statistical analysis of change from baseline in ADCOMS at 18 months – MMRM, Clarity AD Core study, MCI due to AD without symptomatic AD medication at baseline subgroup

Statistic	Lecanemab (n=[redacted])	Placebo (n=[redacted])
Number of patients included in the MMRM	[redacted]	[redacted]
Number of subjects at 18-month visit (week 79)	[redacted]	[redacted]
Mean ADCOMS at baseline (SD)	[redacted]	[redacted]
Adjusted mean change from baseline at 18 months (SE)	[redacted]	[redacted]
Adjusted mean difference (lecanemab – placebo)	[redacted]	
95% confidence interval (CI) for differences	[redacted]	
p-value	[redacted]	
% Difference vs. placebo	[redacted]	

Abbreviations: ADCOMS – Alzheimer's Disease Composite Score; AD – Alzheimer's disease; CI – Confidence interval; MCI – Mild cognitive impairment; MMRM – mixed model for repeated measures; SE – Standard error.
N shows the number of subjects at each visit.
Source: Eisai data on file: Biostatistics analyses for AMNOG

Table 5: Statistical analysis of change from baseline in ADCS MCI-ADL at 18 months – MMRM, Clarity AD Core study, MCI due to AD without symptomatic AD medication at baseline subgroup

Statistic	Lecanemab (n=[redacted])	Placebo (n=[redacted])
Number of patients included in the MMRM	[redacted]	[redacted]
Number of subjects at 18-month visit (week 79)	[redacted]	[redacted]
Mean ADCS MCI-ADL at baseline (SD)	[redacted]	[redacted]
Adjusted mean change from baseline at 18 months (SE)	[redacted]	[redacted]
Adjusted mean difference (lecanemab – placebo)	[redacted]	
95% confidence interval (CI) for differences	[redacted]	
p-value	[redacted]	
% Difference vs. placebo	[redacted]	

Abbreviations: ADCS MCI-ADL – Alzheimer's Disease Cooperative Study-Activities of Daily Living Scale for Mild Cognitive Impairment; AD – Alzheimer's disease; CI – Confidence interval; MCI – Mild cognitive impairment; MMRM – mixed model for repeated measures; SE – Standard error.
N shows the number of subjects at each visit.
Source: Eisai data on file: Biostatistics analyses for AMNOG

Please also provide the equivalent analyses, for all reported outcomes (CDR-SB, ADAS-Cog14, ADCOMS, MMSE and FAQ), for patients in Study 201 who were treated with 10 mg/kg biweekly lecanemab.

Company response: Within Study 201, of the 152 patients randomised to lecanemab 10 mg/kg bi-weekly who had MCI due to AD at baseline, only [redacted] patients

were not treated with symptomatic AD medication at baseline.[1] As such, subgroup analyses were not conducted for this subgroup on the basis of the small sample size.

A 6. PRIORITY QUESTION The decision problem specifies the comparator, for the mild dementia due to AD population, as AChEI plus non-pharmacological management (amended to AChEI and/or non-pharmacological management in the CS).

Please provide subgroup analyses, for all reported outcomes (CDR-SB, ADAS-Cog14, ADCOMS and ADCS MCI-ADL), for participants with mild dementia due to AD, <u>excluding</u>:

a) Those participants who received memantine during the study (consistent with the company's definition of the decision problem)

Company response: The results of subgroup analyses for patients with mild AD excluding those who received memantine during Clarity AD for CDR-SB, ADAS-Cog14, ADCOMS, and ADCS MCI-ADL are presented in Table 6, Table 7, Table 8, and Table 9, respectively. It should be noted that Clarity AD was not powered to detect differences in this subgroup and therefore results should be interpreted with caution.

Table 6: Statistical analysis of change from baseline in CDR-SB at 18 months - MMRM, Clarity AD Core study, mild AD without memantine at baseline

Statistic	Lecanemab ([redacted])	Placebo ([redacted])
Number of patients included in the MMRM	[redacted]	[redacted]
Number of subjects at 18-month visit (week 79)	[redacted]	[redacted]
Mean at baseline (SD)	[redacted]	[redacted]
Adjusted mean at 18 months (SE)	[redacted]	[redacted]
Adjusted mean difference (lecanemab – placebo)	[redacted]	
95% confidence interval (CI) for differences	[redacted]	
p-value	[redacted]	
% Difference vs. placebo	[redacted]	

Abbreviations: AD – Alzheimer's disease; CDR-SB – Clinical Dementia Rating-Sum of Boxes; CI – Confidence interval; MCI – Mild cognitive impairment; MMRM – mixed model for repeated measures; SE – Standard error.
N shows the number of subjects at each visit.
Source: Eisai data on file: Biostatistics analyses for AMNOG

Table 7: Statistical analysis of change from baseline in ADAS-Cog14 at 18 months – MMRM, Clarity AD Core study, mild AD without memantine at baseline

Statistic	Lecanemab ([redacted])	Placebo ([redacted])
Number of patients included in the MMRM	[redacted]	[redacted]
Number of subjects at 18-month visit (week 79)	[redacted]	[redacted]
Mean at baseline (SD)	[redacted]	[redacted]
Adjusted mean at 18 months (SE)	[redacted]	[redacted]
Adjusted mean difference (lecanemab – placebo)	[redacted]	
95% confidence interval (CI) for differences	[redacted]	
p-value	[redacted]	
% Difference vs. placebo	[redacted]	

Abbreviations: ADAS-Cog14 – Alzheimer's Disease Assessment Scale - Cognitive subscale 14-item version; AD – Alzheimer's disease; CI – Confidence interval; MCI – Mild cognitive impairment; MMRM – mixed model for repeated measures; SE – Standard error.
N shows the number of subjects at each visit.
Source: Eisai data on file: Biostatistics analyses for AMNOG

Table 8: Statistical analysis of change from baseline in ADCOMS at 18 months – MMRM, Clarity AD Core study, mild AD without memantine at baseline

Statistic	Lecanemab ([redacted])	Placebo ([redacted])
Number of patients included in the MMRM	[redacted]	[redacted]
Number of subjects at 18-month visit (week 79)	[redacted]	[redacted]
Mean at baseline (SD)	[redacted]	[redacted]
Adjusted mean at 18 months (SE)	[redacted]	[redacted]
Adjusted mean difference (lecanemab – placebo)	[redacted]	
95% confidence interval (CI) for differences	[redacted]	
p-value	[redacted]	
% Difference vs. placebo	[redacted]	

Abbreviations: ADCOMS – Alzheimer's Disease Composite Score; AD – Alzheimer's disease; CI – Confidence interval; MCI – Mild cognitive impairment; MMRM – mixed model for repeated measures; SE – Standard error.
N shows the number of subjects at each visit.
Source: Eisai data on file: Biostatistics analyses for AMNOG

Table 9: Statistical analysis of change from baseline in ADCS MCI-ADL at 18 months – MMRM, Clarity AD Core study, mild AD without memantine at baseline

Statistic	Lecanemab ([redacted])	Placebo ([redacted])
Number of patients included in the MMRM	[redacted]	[redacted]
Number of subjects at 18-month visit (week 79)	[redacted]	[redacted]
Mean at baseline (SD)	[redacted]	[redacted]
Adjusted mean at 18 months (SE)	[redacted]	[redacted]
Adjusted mean difference (lecanemab – placebo)	[redacted]	
95% confidence interval (CI) for differences	[redacted]	
p-value	[redacted]	
% Difference vs. placebo	[redacted]	

Abbreviations: ADCS MCI-ADL – Alzheimer's Disease Cooperative Study-Activities of Daily Living Scale for Mild Cognitive Impairment; AD – Alzheimer's disease; CI – Confidence interval; MCI – Mild cognitive impairment; MMRM – mixed model for repeated measures; SE – Standard error.
N shows the number of subjects at each visit.
Source: Eisai data on file: Biostatistics analyses for AMNOG

b)Those patients who received memantine during the study and those patients who did not receive AChEI during the study (consistent with the final scope)

Company response: The results of subgroup analyses for patients with mild AD excluding those who received memantine and those who did not receive AChEIs during Clarity AD for CDR-SB, ADAS-Cog14, ADCOMS, and ADCS MCI-ADL are presented in Table 10, Table 11, Table 12, and Table 13, respectively. It should be noted that Clarity AD was not powered to detect differences in this subgroup and therefore results should be interpreted with caution.

Table 10: Statistical analysis of change from baseline in CDR-SB at 18 months - MMRM, Clarity AD Core study, mild AD with AChEIs only at baseline

Statistic	Lecanemab (n=164)	Placebo (n=173)
Number of patients included in the MMRM		
Number of subjects at 18-month visit (week 79)		
Mean at baseline (SD)		
Adjusted mean at 18 months (SE)		
Adjusted mean difference (lecanemab – placebo)		
95% confidence interval (CI) for differences		
p-value		
% Difference vs. placebo		

Abbreviations: AD – Alzheimer's disease; CDR-SB – Clinical Dementia Rating-Sum of Boxes; CI – Confidence interval; MCI – Mild cognitive impairment; MMRM – mixed model for repeated measures; SE – Standard error.
N shows the number of subjects at each visit.
Source: Eisai data on file: Biostatistics analyses for AMNOG

Table 11: Statistical analysis of change from baseline in ADAS-Cog14 at 18 months – MMRM, Clarity AD Core study, mild AD with AChEIs only at baseline

Statistic	Lecanemab (n=164)	Placebo (n=173)
Number of patients included in the MMRM		
Number of subjects at 18-month visit (week 79)		
Mean at baseline (SD)		
Adjusted mean at 18 months (SE)		
Adjusted mean difference (lecanemab – placebo)		
95% confidence interval (CI) for differences		
p-value		
% Difference vs. placebo		

Abbreviations: ADAS-Cog14 – Alzheimer's Disease Assessment Scale - Cognitive subscale 14-item version; AD – Alzheimer's disease; CI – Confidence interval; MCI – Mild cognitive impairment; MMRM – mixed model for repeated measures; SE – Standard error.
N shows the number of subjects at each visit.
Source: Eisai data on file: Biostatistics analyses for AMNOG

Table 12: Statistical analysis of change from baseline in ADCOMS at 18 months – MMRM, Clarity AD Core study, mild AD with AChEIs only at baseline

Statistic	Lecanemab (n=164)	Placebo (n=173)
Number of patients included in the MMRM	[redacted]	[redacted]
Number of subjects at 18-month visit (week 79)	[redacted]	[redacted]
Mean at baseline (SD)	[redacted]	[redacted]
Adjusted mean at 18 months (SE)	[redacted]	[redacted]
Adjusted mean difference (lecanemab – placebo)	[redacted]	
95% confidence interval (CI) for differences	[redacted]	
p-value	[redacted]	
% Difference vs. placebo	[redacted]	

Abbreviations: ADCOMS – Alzheimer's Disease Composite Score; AD – Alzheimer's disease; CI – Confidence interval; MCI – Mild cognitive impairment; MMRM – mixed model for repeated measures; SE – Standard error.
N shows the number of subjects at each visit.
Source: Eisai data on file: Biostatistics analyses for AMNOG

Table 13: Statistical analysis of change from baseline in ADCS MCI-ADL at 18 months – MMRM, Clarity AD Core study, mild AD with AChEIs only at baseline

Statistic	Lecanemab (n=164)	Placebo (n=173)
Number of patients included in the MMRM	[redacted]	[redacted]
Number of subjects at 18-month visit (week 79)	[redacted]	[redacted]
Mean at baseline (SD)	[redacted]	[redacted]
Adjusted mean at 18 months (SE)	[redacted]	[redacted]
Adjusted mean difference (lecanemab – placebo)	[redacted]	
95% confidence interval (CI) for differences	[redacted]	
p-value	[redacted]	
% Difference vs. placebo	[redacted]	

Abbreviations: ADCS MCI-ADL – Alzheimer's Disease Cooperative Study-Activities of Daily Living Scale for Mild Cognitive Impairment; AD – Alzheimer's disease; CI – Confidence interval; MCI – Mild cognitive impairment; MMRM – mixed model for repeated measures; SE – Standard error.
N shows the number of subjects at each visit.
Source: Eisai data on file: Biostatistics analyses for AMNOG

Please also provide the equivalent analyses, for all reported outcomes (CDR-SB, ADAS-Cog14, ADCOMS, MMSE and FAQ), for patients in Study 201 who were treated with 10 mg/kg biweekly lecanemab.

Company response: Within Study 201, of the 152 patients randomised to lecanemab treated with 10 mg/kg who had mild AD at baseline, [redacted] patients were not receiving memantine treatment at baseline (the sample size for part a), and only [redacted] patients were treated with an AChEI alone at baseline (the sample size for part a).

As such, subgroup analyses were not conducted for these subgroups on the basis of the small sample sizes.

A 7. The comparator, specified in the final scope and in the company's definition of the decision problem, includes non-pharmacological management for both clinical populations (MCI due to AD and mild dementia due to AD).

Please provide:

a) **The numbers of participants who received non-pharmacological interventions during the Clarity AD study, by study arm (lecanemab and placebo) and by clinical subgroup (MCI due to AD and mild dementia due to AD).**

Company response: Table 14 presents the number of patients who received non-pharmacological interventions by study arm and clinical subgroup.

Table 14: Non-pharmacological interventions by study arm and clinical subgroup, Clarity AD

Clinical subgroup	Lecanemab, n	Placebo, n
All patients	[redacted]	[redacted]
MCI due to AD	[redacted]	[redacted]
Mild AD	[redacted]	[redacted]

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

b) **Details of any non-pharmacological interventions received by participants in the Clarity AD study, by study arm (lecanemab and placebo) and by clinical subgroup (MCI due to AD and mild dementia due to AD).**

Company response: "Non-pharmacological interventions" such as cognitive training, cognitive stimulation, and reminiscence therapy were not recorded in Clarity AD. "Non-pharmacological procedures" captured in Clarity AD included any type of medical procedures that were not therapeutic medications. This consisted of all types of procedures, including those to treat diseases other than AD such as skin grafting and excision of melanoma. As such, these data have not been provided.

A 8. The company submission (CS) (Table 1, pg 10) states that the outcomes in the decision problem addressed by the CS were *'in line with scope'*, however, the CS does not include any data for the outcomes *'non-cognitive symptoms (behavioural and psychiatric'* or *'admission to full-time care'.*

Please confirm that there are no data available to inform the effects of lecanemab on these outcome measures or provide any data which are available.

Company response: Data on admission to full-time care was not collected in Clarity AD, hence suitable data was identified from the published literature to inform health state-specific rates of institutionalisation, as detailed in the CS, Document B, Section B.3.3.4.

Data on patient anxiety/depression is available from Clarity AD, as part of the EQ-5D-5L domains (Table 15). Additionally, data on patient mood is available as part of the QOL-AD domains (Table 16).

Table 15: Statistical analysis of change from baseline in EQ-5D-5L – anxiety/depression at 18 months – MMRM, Clarity AD Core study, ITT FAS+

Statistic	Lecanemab (n=859)	Placebo (n=875)
Number of patients included in the MMRM	[redacted]	[redacted]
Number of subjects at 18-month visit (week 79)	[redacted]	[redacted]
Mean at baseline (SD)	[redacted]	[redacted]
Adjusted mean at 18 months in MMRM (SE)	[redacted]	[redacted]
Adjusted mean difference (lecanemab – placebo)	[redacted]	
95% confidence interval (CI) for differences	[redacted]	
p-value	[redacted]	
% Difference vs. placebo	[redacted]	

Abbreviations: CI – Confidence interval; FAS+ - Full Analysis Set+; ITT – intent-to-treat; MMRM – mixed model for repeated measures; SE – Standard error.
N shows the number of subjects at each visit.
Source: Clarity AD CSR Table 14.2.3.4.2[2]

Table 16: Statistical analysis of change from baseline in QOL-AD – mood at 18 months – MMRM, Clarity AD Core study, ITT FAS+

Statistic	Lecanemab (n=859)	Placebo (n=875)
Number of patients included in the MMRM	[redacted]	[redacted]
Number of subjects at 18-month visit (week 79)	[redacted]	[redacted]
Mean at baseline (SD)	[redacted]	[redacted]
Adjusted mean at 18 months in MMRM (SE)	[redacted]	[redacted]
Adjusted mean difference (lecanemab – placebo)	[redacted]	
95% confidence interval (CI) for differences	[redacted]	
p-value	[redacted]	
% Difference vs. placebo	[redacted]	

Abbreviations: CI – Confidence interval; FAS+ - Full Analysis Set+; ITT – intent-to-treat; MMRM – mixed model for repeated measures; QOL – Quality of life in Alzheimer's Disease; SE – Standard error.
N shows the number of subjects at each visit.
Source: Clarity AD CSR Table 14.2.3.5.2[2]

Whilst C-SSRS was also collected in Clarity AD, this was collected as part of the safety assessment, rather than to identify non-cognitive symptoms. More generally EMA guideline on the clinical investigation of medicines for the treatment of AD delineates behavioral and psychiatric symptoms to be assessed in patients with severe dementia due to AD, as behavioral problems have a major impact on patients and carers in advanced stages of dementia, rather than early AD.[3]

A 9. The company submission (CS) (Table 1, pg 10) states, under subgroups to be considered, that *'scenario analyses for MCI due to AD and mild dementia due to AD are presented'*.

Please provide equivalent scenario analyses for apolipoprotein E4 gene carrier status.

Company response: Results for the requested scenario are presented Table 54. The *APOE4* non-carrier subgroup scenario results in a decrease of [redacted] compared with the corrected base-case list price ICER, to [redacted]. The associated PAS ICER is in this scenario is [redacted]. The *APOE4* homozygous subgroup scenario results in [redacted] compared with the corrected base-case list price ICER, to [redacted]. The associated PAS ICER is in this scenario is [redacted]. The *APOE4* heterozygous subgroup scenario results in [redacted] compared with

the corrected base-case list price ICER, to [redacted]. The associated PAS ICER is in this scenario is £[redacted].

In each analysis, the following *APOE4* subgroup data is used:

- Time to worsening HR

Table 17: Time to worsening by *APOE4* status

	Non-carriers	Heterozygotes	Homozygotes
HR (95% CI)	[redacted]	[redacted]	[redacted]

Abbreviations: CI, confidence interval; HR, hazard ratio.

- Patient counts, 0-18 months

Table 18: Clarity AD, Summary of Counts for Subjects in Each Health State Using CDR-SB, Core Study, *APOE4* non-carriers

Baseline state	MCI due to AD n (%)	Mild AD n (%)	Moderate AD n (%)	Severe AD n (%)
Lecanemab				
[redacted]				
Placebo				
[redacted]				

Abbreviations: AD, Alzheimer's disease; FAS, full analysis set; ITT, intention-to-treat; MCI, mild cognitive impairment.

Table 19: Clarity AD, Summary of Counts for Subjects in Each Health State Using CDR-SB, Core Study, *APOE4* Heterozygous Carriers.

Baseline state	MCI due to AD n (%)	Mild AD n (%)	Moderate AD n (%)	Severe AD n (%)
Lecanemab				
[redacted]				
Placebo				
[redacted]				

Abbreviations: AD, Alzheimer's disease; FAS, full analysis set; ITT, intention-to-treat; MCI, mild cognitive impairment.

Table 20: Clarity AD, Summary of Counts for Subjects in Each Health State Using CDR-SB, Core Study, *APOE4* Homozygous carriers.

Baseline state	MCI due to AD n (%)	Mild AD n (%)	Moderate AD n (%)	Severe AD n (%)
Lecanemab				
[redacted]				
Placebo				
[redacted]				

Abbreviations: AD, Alzheimer's disease; FAS, full analysis set; ITT, intention-to-treat; MCI, mild cognitive impairment

- Adverse events

Table 21: Adverse event frequencies by *APOE4* status, Core study

Event	Severity*	Lecanemab	SoC
Non-carriers			
Infusion-related reaction	Mild	[redacted]	[redacted]
	Moderate	[redacted]	[redacted]
	Severe	[redacted]	[redacted]
	Serious	[redacted]	[redacted]
ARIA-E	Mild	[redacted]	[redacted]
	Moderate	[redacted]	[redacted]
	Severe	[redacted]	[redacted]
	Serious	[redacted]	[redacted]

ARIA-H	Mild	[redacted]	[redacted]
	Moderate	[redacted]	[redacted]
	Severe	[redacted]	[redacted]
	Serious	[redacted]	[redacted]
Heterozygotes			
Infusion-related reaction	Mild	[redacted]	[redacted]
	Moderate	[redacted]	[redacted]
	Severe	[redacted]	[redacted]
	Serious	[redacted]	[redacted]
ARIA-E	Mild	[redacted]	[redacted]
	Moderate	[redacted]	[redacted]
	Severe	[redacted]	[redacted]
	Serious	[redacted]	[redacted]
ARIA-H	Mild	[redacted]	[redacted]
	Moderate	[redacted]	[redacted]
	Severe	[redacted]	[redacted]
	Serious	[redacted]	[redacted]
Homozygotes			
Infusion-related reaction	Mild	[redacted]	[redacted]
	Moderate	[redacted]	[redacted]
	Severe	[redacted]	[redacted]
	Serious	[redacted]	[redacted]
ARIA-E	Mild	[redacted]	[redacted]
	Moderate	[redacted]	[redacted]
	Severe	[redacted]	[redacted]
	Serious	[redacted]	[redacted]
ARIA-H	Mild	[redacted]	[redacted]
	Moderate	[redacted]	[redacted]
	Severe	[redacted]	[redacted]
	Serious	[redacted]	[redacted]

Abbreviations: AE , Adverse event; ARIA-E , amyloid-related imaging abnormality-oedema/effusion; ARIA-H, amyloid-related imaging abnormality-microhaemorrhage and haemosiderin deposit.
*ARIA-E and ARIA-H based on maximum radiographic severity. Infusion-related reactions are based on NCI-CTCAE criteria; mild = grade 1, moderate = grade 2, severe = grade 3, serious = grade 4

- Compliance

Table 22: Compliance by *APOE4* status

	Non-carriers	Heterozygotes	Homozygotes
Mean (SD)	[redacted]	[redacted]	[redacted]

Abbreviations: SD, standard deviation.

- All-cause discontinuation, calculated as the number of discontinuation events divided by the total duration of exposure in subject years

Table 23: Exposure and discontinuation events by *APOE4* status

	Non-carriers	Heterozygotes	Homozygotes
Total duration	[redacted]	[redacted]	[redacted]
Number of discontinuation events	[redacted]	[redacted]	[redacted]

- Mean patient weight

Table 24: Mean patient weight by *APOE4* status

	Non-carriers	Heterozygotes	Homozygotes
Mean (SD)	[redacted]	[redacted]	[redacted]

Abbreviations: SD, standard deviation

The time to worsening analysis was not conducted separately for patients who were MCI due to AD and mild AD at baseline due to low patient numbers in the *APOE4* subgroups. Instead, a single, pooled HR for patients in the MCI due to AD and mild AD health states was estimated.

Table 25: Baseline health state - *APOE4* subgroups, Core study, ITT FAS+

Baseline health state	Non-carriers		Homozygotes		Heterozygotes	
	Lecanemab	Placebo	Lecanemab	Placebo	Lecanemab	Placebo
MCI due to AD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mild AD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AD – Alzheimer's disease; APOE4 - apolipoprotein E4; FAS – Full Analysis Set; ITT – intent to treat; MCI – mild cognitive impairment

Systematic review

A 10. The inclusion criteria for outcomes (Table 11, Appendix D1.2) were based on the outcomes measured in the Clarity AD study (rather than those listed in the final scope).

Please provide a justification for this choice.

Company response: The outcomes/endpoints utilised in the search strategy are widely explored in AD clinical trials as a global measure of disease progression. They comprise well-established clinical tools, important to demonstrate the effect of

DMTs in the AD treatment landscape. The EMA guideline on the clinical investigation of medicines for the treatment of AD was taken into consideration for the selection of outcomes/endpoints for the search, as well as the outcomes measured in Clarity AD.

The company believe the outcomes included in the clinical SLR effectively covers the overall impact of early AD on patients and carers. CDR-SB, Global CDR, and ADAS-Cog cover cognitive and functional impairment aspects, whilst degree of independence is captured through ADCS-ADL. Cognition, function, and overall clinical response are the domains the EMA guideline on the clinical investigation of medicines for the treatment of AD has identified to assess for efficacy of a treatment in patients with MCI due to AD or mild dementia due to AD. Behavioural and psychiatric symptoms are less pertinent to early AD, as supported by the EMA guideline, which suggests those symptoms to be assessed in severe dementia due to AD.[3]

In addition, overall and treatment-specific adverse effects were considered, including subjects discontinuing due to mortality or adverse effects. HRQoL evaluation was formally conducted through a separate SLR (refer to CS, Appendix H).[4]

A 11. The PRISMA flow chart provided in the CS (Figure 6, appendix D1.2) indicates that 157 studies were excluded for *'objective outcome not of interest'*.

Please provide details of any of these studies, excluded for *'outcome not of interest'* that reported an outcome listed in the final scope.

Company response: The 157 studies excluded in the SLR due to 'objective outcome not of interest' have been reviewed against the outcomes listen in the final NICE scope. The company can confirm that none of these studies evaluated any relevant outcome listed in the NICE final scope.

A 12. The PRISMA flow chart provided in the CS (Figure 6, appendix D1.2) indicates that 101 studies were excluded for *'comparator one treatment arm not of interest'*.

Please confirm that none of these studies included treatment arms that could provide a relevant comparison (in addition to any non-relevant arms).

Company response: We confirm that none of the studies excluded based on *'comparator one treatment arm not of interest'* provided a comparison relevant to the decision problem. Per the SLR inclusion criteria, studies that compared at least two relevant treatment arms of interest were included, i.e., studies with all non-relevant treatment arms or only one relevant treatment arm were excluded.

Clinical effectiveness evidence

A 13. PRIORITY QUESTION The CS (sections B.2.6.1 and B.2.6.2) reports primary and secondary clinical outcomes (CDR-SB, ADAS-Cog14, ADCOMS and ADCS MCI-ADL) as adjusted mean change from baseline (to 18 months) and adjusted mean difference in change from baseline (lecanemab vs. placebo).

For all clinical outcomes reported (CDR-SB, ADAS-Cog14, ADCOMS and ADCS MCI-ADL), and for all subgroup analyses, please provide mean baseline and end-point (18 month) for both the lecanemab and placebo groups.

Company response: The mean baseline and 18-month end-points from Clarity AD for the ITT FAS+ population are presented in Table 26 to Table 29, and the equivalent results for all subgroup analysis (including MCI due to AD, Mild AD, *APOE4* carriers and non-carriers, *APOE4* heterozygous carriers and *APOE4* homozygous carriers) are presented in Table 30 to Table 33 for CDR-SB, ADAS-Cog14, ADCOMS and ADCS MCI-ADL, respectively. Please note, the adjusted mean change is estimated from the MMRM and therefore does not align in all instances with the mean baseline and mean 18-month values.

Table 26: Statistical analysis of change from baseline in CDR-SB at 18 months - MMRM, Clarity AD Core study, ITT FAS+

CDR-SB	Lecanemab (n=859)	Placebo (n=875)
Number of patients included in the MMRM	859	875
N (week 79)	714	757
Baseline mean (SD)	[redacted]	[redacted]
18-month mean (SD)		
Adjusted mean change from baseline in MMRM (SE)	1.213 (0.082)	1.663 (0.080)
Adjusted mean difference in change from baseline (lecanemab – placebo)	-0.451	
95% confidence interval (CI) for differences	-0.669, -0.233	
p-value	0.00005	

% Difference vs. placebo	-27.1%

Abbreviations: CDR-SB - Clinical Dementia Rating-Sum of Boxes; CI – confidence interval; SD – standard deviation; SE – standard error; MMRM – mixed model for repeated measures

Table 27: Statistical analysis of change from baseline in ADAS-Cog14 at 18 months – MMRM, Clarity AD Core study, ITT FAS+

ADAS-Cog14	Lecanemab (n=859)	Placebo (n=875)
Number of patients included in the MMRM	856	873
N (week 79)	705	740
Baseline mean (SD)	[redacted]	[redacted]
18-month mean (SD)	[redacted]	[redacted]
Adjusted mean change from baseline in MMRM (SE)	4.140 (0.314)	5.581 (0.309)
Adjusted mean difference in change from baseline (lecanemab – placebo)	-1.442	
95% confidence interval (CI) for differences	-2.270, -0.613	
p-value	0.00065	
% Difference vs. placebo	-25.8%	

Abbreviations: ADAS-Cog14 – Alzheimer's Disease Assessment Scale - Cognitive Subscale 14-item version; CI – confidence interval; SD – standard deviation; SE – standard error; MMRM – mixed model for repeated measures

Table 28: Statistical analysis of change from baseline in ADCOMS at 18 months – MMRM, Clarity AD Core study, ITT FAS+

ADCOMS	Lecanemab (n=859)	Placebo (n=875)
Number of patients included in the MMRM	859	875
N (week 79)	705	749
Baseline mean (SD)	[redacted]	[redacted]
18-month mean (SD)	[redacted]	[redacted]
Adjusted mean change from baseline in MMRM (SE)	0.164 (0.009)	0.214 (0.009)
Adjusted mean difference in change from baseline (lecanemab – placebo)	-0.050	
95% confidence interval (CI) for differences	-0.074, -0.027	
p-value	0.00002	
% Difference vs. placebo	-23.5%	

Abbreviations: ADCOMS – Alzheimer's Disease Composite Score; CI – confidence interval; SD – standard deviation; SE – standard error; MMRM – mixed model for repeated measures

Table 29: Statistical analysis of change from baseline in ADCS MCI-ADL at 18 months – MMRM, Clarity AD Core study, ITT FAS+

ADAS-Cog14	Lecanemab (n=859)	Placebo (n=875)
Number of patients included in the MMRM	808	822
N (week 79)	715	754
Baseline mean (SD)	[redacted]	[redacted]
18-month mean (SD)	[redacted]	[redacted]
Adjusted mean change from baseline in MMRM (SE)	-3.484 (0.313)	-5.500 (0.308)
Adjusted mean difference in change from baseline (lecanemab – placebo)	2.016	

95% confidence interval (CI) for differences	1.208, 2.823
p-value	<.00001
% Difference vs. placebo	-36.6%

Abbreviations: ADCS MCI-ADL – Alzheimer's Disease Cooperative Study-Activities of Daily Living Scale for Mild Cognitive Impairment; CI – confidence interval; SD – standard deviation; SE – standard error; MMRM – mixed model for repeated measures

Table 30: Summary of baseline and 18-months CDR-SB by subgroup –Clarity AD Core study, ITT FAS+

CDR-SB	MCI due to AD		Mild AD		*APOE4* non carriers		*APOE4* carriers		*APOE4* Heterozygous Carriers		*APOE4* Homozygous Carriers	
	Lecanemab (n=528)	Placebo (n=544)	Lecanemab (n=331)	Placebo (n=331)	Lecanemab (n=267)	Placebo (n=275)	Lecanemab (n=592)	Placebo (n=600)	Lecanemab (n=456)	Placebo (n=468)	Lecanemab (n=136)	Placebo (n=132)
N (baseline)	[redacted]											
N (week 79)	[redacted]											
Baseline mean (SD)	[redacted]											
18-month mean (SD)	[redacted]											

Abbreviations: AD – Alzheimer's disease; *APOE4* - apolipoprotein E4; CDR-SB - Clinical Dementia Rating-Sum of Boxes; SD – standard deviation; MCI – mild cognitive impairment;

Table 31: Statistical analysis of change from baseline and 18 months in ADAS-Cog14 by subgroup – Clarity AD Core study, ITT FAS+

ADAS-Cog14	MCI due to AD		Mild AD		*APOE4* non carriers		*APOE4* carriers		*APOE4* Heterozygous Carriers		*APOE4* Homozygous Carriers	
	Lecanemab (n=528)	Placebo (n=544)	Lecanemab (n=331)	Placebo (n=331)	Lecanemab (n=267)	Placebo (n=275)	Lecanemab (n=592)	Placebo (n=600)	Lecanemab (n=456)	Placebo (n=468)	Lecanemab (n=136)	Placebo (n=132)
N (baseline)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
N (week 79)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Baseline mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
18-month mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AD – Alzheimer's disease; ADAS-Cog14 – Alzheimer's Disease Assessment Scale - Cognitive Subscale 14-item version; *APOE4* - apolipoprotein E4; SD – standard deviation; MCI – mild cognitive impairment;

Table 32: Statistical analysis of change from baseline and 18-months in ADCOMS by subgroup – Clarity AD Core study, ITT FAS+

ADCOMS	MCI due to AD		Mild AD		*APOE4* non carriers		*APOE4* carriers		*APOE4* Heterozygous Carriers		*APOE4* Homozygous Carriers	
	Lecanemab (n=528)	Placebo (n=544)	Lecanemab (n=331)	Placebo (n=331)	Lecanemab (n=267)	Placebo (n=275)	Lecanemab (n=592)	Placebo (n=600)	Lecanemab (n=456)	Placebo (n=468)	Lecanemab (n=136)	Placebo (n=132)
N (baseline)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
N (week 79)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Baseline mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
18-month mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AD – Alzheimer's disease; ADCOMS - Alzheimer's Disease Composite Score; *APOE4* - apolipoprotein E4; MCI – mild cognitive impairment;

Table 33: Statistical analysis of change from baseline and 18-months in ADCS MCI-ADL by subgroup –Clarity AD Core study, ITT FAS+

ADCS MCI-ADL	MCI due to AD		Mild AD		*APOE4* non carriers		*APOE4* carriers		*APOE4* Heterozygous Carriers		*APOE4* Homozygous Carriers	
	Lecanemab (n=528)	Placebo (n=544)	Lecanemab (n=331)	Placebo (n=331)	Lecanemab (n=267)	Placebo (n=275)	Lecanemab (n=592)	Placebo (n=600)	Lecanemab (n=456)	Placebo (n=468)	Lecanemab (n=136)	Placebo (n=132)
N(baseline)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
N (week 79)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Baseline mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
18-month mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AD – Alzheimer's disease; ADCS MCI-ADL – Alzheimer's Disease Cooperative Study-Activities of Daily Living Scale for Mild Cognitive Impairment; *APOE4* - apolipoprotein E4; MCI – mild cognitive impairment.

Please also provide the equivalent data for all outcomes reported at the 18 month time point (CDR-SB, ADAS-Cog14, ADCOMS, MMSE and FAQ) for patients in Study 201 who were treated with 10 mg/kg biweekly lecanemab.

Please also provide estimates of treatment effect (lecanemab vs. placebo), with confidence intervals, for all outcomes reported at the 18 month time point (CDR-SB, ADAS-Cog14, ADCOMS, MMSE and FAQ), for patients in Study 201 who were treated with 10 mg/kg biweekly lecanemab.

Company response (parts b and c): The mean baseline data, 18-month data, and estimates of treatment effect for all outcomes reported in Study 201 are presented in Table 34.

Table 34: Mean baseline and 18-month results for patients treated with lecanemab 10 mg/kg bi-weekly (Study 201, ITT FAS)

Statistic	Lecanemab 10 mg/kg bi-weekly, n				
	ADCOMS	ADAS-Cog14	MMSE	CDR-SB	FAQ
Number of patients included in the MMRM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
N (week 79)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Baseline mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
18-month mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean change from baseline in MMRM (SE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Least-squares mean difference (lecanemab – placebo)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
90% CI for differences	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
p-value	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ADAS-Cog14 – Alzheimer's Disease Assessment Scale – Cognitive Subscale 14 item version; ADCOMS – Alzheimer's Disease Composite Score; CDR-SB - Clinical Dementia Rating-Sum of Boxes; CI – confidence interval; FAS – Full Analysis Set; FAQ – Functional Assessment Questionnaire ITT – intent to treat; MMRM – mixed model for repeated measures; MMSE – mini mental state examination; SD – standard deviation; SE – standard error.

A 14. PRIORITY QUESTION The CS (section B.2.1.1) provides some details about the OLE of Clarity AD.

Please provide and results from early data cuts from this study or confirm that no follow-up data are yet available from the OLE.

Company response: Interim efficacy results from the Clarity AD OLE based on a data cut-off of 13 March 2023, which provides 6 months of follow-up (24 months including the Clarity AD core study) were presented at the Clinical Trials on Alzheimer's Disease conference (CTAD) meeting in October 2023.[5]

These efficacy results are presented in the form of a delayed start analysis, which compares the following groups:

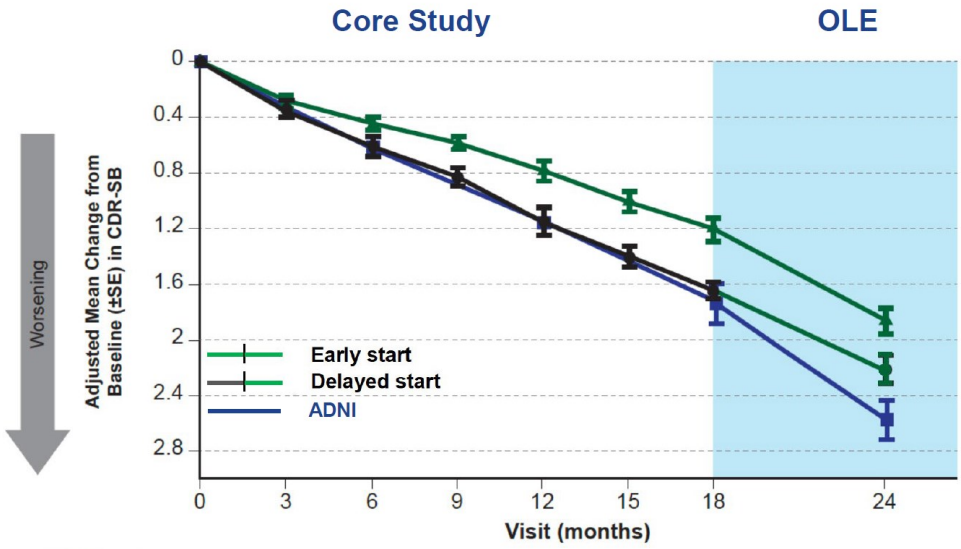
- Early start lecanemab (those treated with lecanemab during the core study)
- Delayed start lecanemab (those treated with placebo in the core study who switched to lecanemab in the OLE)

A non-inferiority test between early start lecanemab and delayed start lecanemab demonstrated that at 24-months, there was [redacted] less decline on adjusted mean change from baseline in CDR-SB for the early start lecanemab group compared with the delayed start lecanemab group. Additionally, non-inferiority criteria were met at 24 months for these groups, with the lower bound of 1-sided 90% CI being greater than 0 (90% CI: [redacted]). Figure 1 demonstrates that the early start lecanemab maintained a separation from the delayed start lecanemab group at 6 months of the OLE phase, and therefore supporting the disease modifying effect of lecanemab. Similar results can be observed for ADAS-Cog14 and ADCS MCI-ADL, in Figure 2 and Figure 3, respectively.

However, it should be noted that comparisons of the early and delayed start groups beyond 18 months are irrelevant to the decision problem given both groups are receiving lecanemab. In relation, the interim efficacy results for CDR-SB were also compared with an observational cohort from the Alzheimer’s Disease Neuroimaging Initiative (ADNI) database (Figure 1). In this analysis, participants from ADNI were

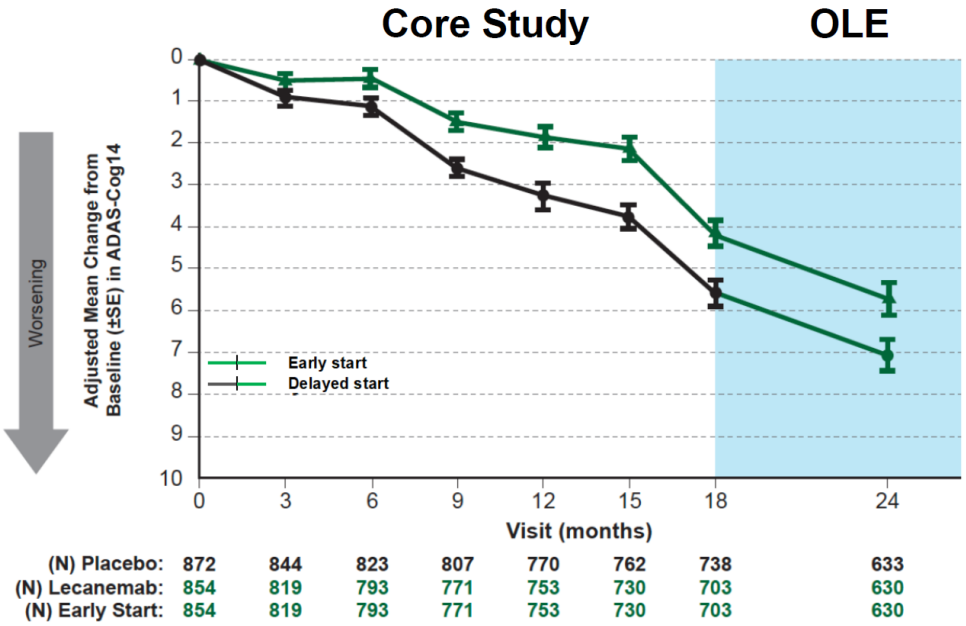
matched with the Clarity AD population based on baseline demographics and clinical characteristics, including randomisation strata. During the core study period, the adjusted mean change from baseline in CDR-SB in the ADNI cohort was similar to the placebo arm. Beyond 18 months, the rate of decline in the ADNI cohort was greater than the delayed start group, consistent with the latter receiving lecanemab from this time point. Although limitations in the generalisability of ADNI to the UK setting were cited in the CS, this comparison nonetheless indicates the treatment effect of lecanemab vs. placebo is maintained beyond the 18-month core study period.

Figure 1: Change in CDR-SB Score through 24 months in Clarity AD OLE study



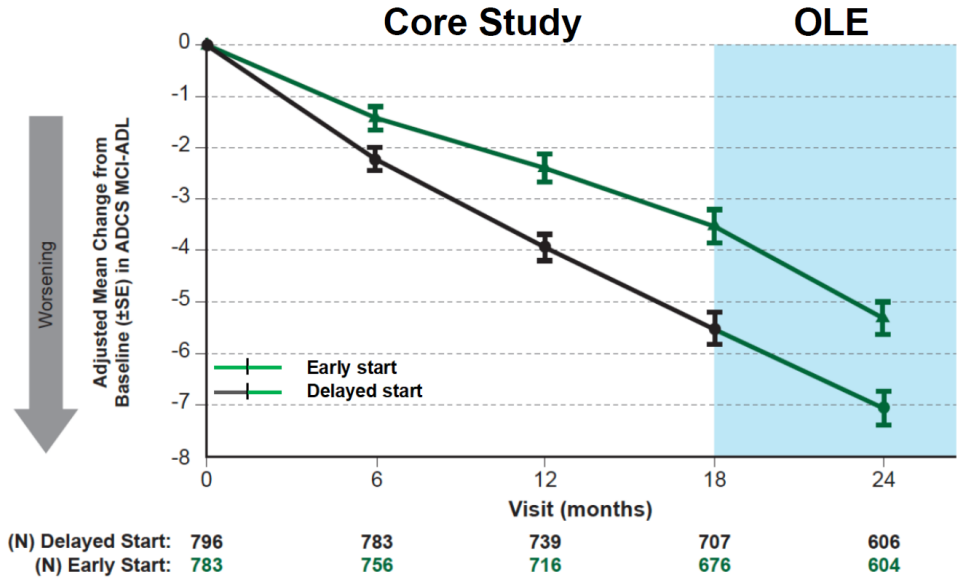
Abbreviations: AD – Alzheimer's disease; CDR-SB – Clinical Dementia Rating Sum of Boxes; OLE – Open label extension
Source: Eisai CTAD Presentation 2023[5]

Figure 2: Change in ADAS-Cog14 score through 24 months in Clarity AD OLE study



Abbreviations: AD – Alzheimer's Disease; ADAS-Cog14 – Alzheimer's Disease Assessment Scale – Cognitive Subscale 14; OLE – Open Label Extension
Source: Eisai CTAD Presentation 2023[5]

Figure 3: Change in ADCS MCI-ADL score through 24 months in Clarity AD OLE study



Abbreviations: AD – Alzheimer's Disease; ADCS MCI-ADL – Alzheimer's Disease Cooperative Study-Activities of Daily Living Inventory Mild Cognitive Impairment Version; OLE – Open Label Extension
Source: Eisai CTAD Presentation 2023[5]

A 15. The CS (section B.2.6.4 and appendix O1.3) describes some study results for the exploratory endpoint *'time to worsening of global CDR score'*. Section B.2.6.4 of the CS defines worsening of global CDR score as *'the first increase*

from baseline by at least 0.5 points on the global CDR score in two consecutive visits' **and presents a hazard ratio which is described as representing** ***'a statistically significant reduction in the risk of progression to the next stage of AD on the global CDR score'*****. It is unclear whether the method used to define** ***'progression to the next stage of AD'*** **was consistent with the standard definitions for the global CDR score (i.e. a change from 0.5 to 1.0 for progression from MCI due to AD to mild dementia due to AD, and a change from 1.0 to 2.0 for progression from mild dementia due to AD to moderate dementia due to AD.**

Please provide:

a) The numbers of participants, in each study arm (lecanemab and placebo) who progressed from MCI due to AD (CDR score 0.5) to mild dementia due to AD (CDR score 1.0), moderate dementia due to AD (CDR score 2.0) and severe dementia due to AD (CDR score 3.0) during the 18-month study period.

Company response: See response to b).

b) The number of participants, in each study arm (lecanemab and placebo) who progressed from mild dementia due to AD (CDR score 1.0) to moderate dementia due to AD (CDR score 2.0) and severe dementia dues to AD (CDR score 3.0) during the 18-month study period.

Company response: In Clarity AD, health state is defined using Global CDR scores as follows: MCI due to AD=0.5, mild AD=1.0, moderate AD=2.0, severe AD=3.0. For MCI due to AD defined by baseline global CDR=0.5, the increase from baseline by at least 0.5 points on the global score indicates global CDR=1, 2, or 3 (mild AD, moderate AD or severe AD).

For Mild AD defined by baseline global CDR=1.0, the minimum increase is 1.0 based on the possible values on the global CDR score (0, 0.5, 1, 2, 3), and the increase from baseline by at least 0.5 points on the global score indicates global CDR=2 or 3 (moderate AD or severe AD).

The numbers of patients in the lecanemab and placebo arms who progressed from MCI due to AD to mild dementia due to AD, moderate dementia due to AD, and severe dementia due AD (as defined by Global CDR score) and the number of patients who progressed from mild dementia due to AD to moderate dementia due to AD and severe dementia due to AD at each visit in Clarity AD are presented in Table 35.

Table 35: Progression from MCI due to AD and mild AD health states within Clarity AD as defined by Global CDR by visit, Core study, ITT FAS+

Visit	Baseline state	Proportion, n		Health state at corresponding visit	Proportion, n (%)	
		Placebo	Lecanemab		Placebo	Lecanemab
Week 13	MCI due to AD	[redacted]	[redacted]	Mild AD	[redacted]	[redacted]
				Moderate AD	[redacted]	[redacted]
				Severe AD	[redacted]	[redacted]
	Mild AD	[redacted]	[redacted]	Moderate AD	[redacted]	[redacted]
				Severe AD	[redacted]	[redacted]
Week 27	MCI due to AD	[redacted]	[redacted]	Mild AD	[redacted]	[redacted]
				Moderate AD	[redacted]	[redacted]
				Severe AD	[redacted]	[redacted]
	Mild AD	[redacted]	[redacted]	Moderate AD	[redacted]	[redacted]
				Severe AD	[redacted]	[redacted]
Week 39	MCI due to AD	[redacted]	[redacted]	Mild AD	[redacted]	[redacted]
				Moderate AD	[redacted]	[redacted]
				Severe AD	[redacted]	[redacted]
	Mild AD	[redacted]	[redacted]	Moderate AD	[redacted]	[redacted]
				Severe AD	[redacted]	[redacted]
Week 53	MCI due to AD	[redacted]	[redacted]	Mild AD	[redacted]	[redacted]
				Moderate AD	[redacted]	[redacted]
				Severe AD	[redacted]	[redacted]
	Mild AD	[redacted]	[redacted]	Moderate AD	[redacted]	[redacted]
				Severe AD	[redacted]	[redacted]
Week 65	MCI due to AD	[redacted]	[redacted]	Mild AD	[redacted]	[redacted]
				Moderate AD	[redacted]	[redacted]
				Severe AD	[redacted]	[redacted]
	Mild AD	[redacted]	[redacted]	Moderate AD	[redacted]	[redacted]
				Severe AD	[redacted]	[redacted]

Week 79	MCI due to AD	[redacted]	[redacted]	Mild AD	[redacted]	[redacted]
				Moderate AD	[redacted]	[redacted]
				Severe AD	[redacted]	[redacted]
	Mild AD	[redacted]	[redacted]	Moderate AD	[redacted]	[redacted]
				Severe AD	[redacted]	[redacted]
Week 81	MCI due to AD	[redacted]	[redacted]	Mild AD	[redacted]	[redacted]
				Moderate AD	[redacted]	[redacted]
				Severe AD	[redacted]	[redacted]
	Mild AD	[redacted]	[redacted]	Moderate AD	[redacted]	[redacted]
				Severe AD	[redacted]	[redacted]

Abbreviations: AD – Alzheimer's disease; FAS+ - Full Analysis Set+; ITT – intent-to-treat; MCI – mild cognitive impairment.
Source: Clarity AD CSR Tables 14.2.3.7.1 and 14.2.3.7.2[2]

A 16. The CS (Table 63, appendix O1.1) provides some information about concomitant medications taken by participants in the Clarity AD trial, however, further stratification is needed to fully assess the comparability of the trial to UK clinical practice and to the final scope.

Please complete the following table:

Company response: Table 36 has been completed for the first four rows. "Non-pharmacological procedures" captured in Clarity AD included any type of medical procedures that were not therapeutic medications. This consisted of procedures outside of those used to treated AD, including those as skin grafting and excision of melanoma. The type of "non-pharmacological interventions" such as cognitive training, cognitive stimulation, and reminiscence therapy were not recorded in Clarity AD. As such, we are unable to complete the final three rows of the table.

Table 36: Patients who received concomitant medication in Clarity AD, SAS

	Number of patients, n (%)			
	Lecanemab (n=898)		**Placebo (n=897)**	
	MCI (n=552)	**Mild AD (n=346)**	**MCI (n=555)**	**Mild AD (n=342)**
Patients who received an AChEI	[redacted]	[redacted]	[redacted]	[redacted]
Patients who received memantine	[redacted]	[redacted]	[redacted]	[redacted]
Patients who received an AChEI AND memantine	[redacted]	[redacted]	[redacted]	[redacted]

Patients who received a non-pharmacological intervention (e.g. cognitive training, cognitive stimulation, reminiscence therapy)	[redacted]	[redacted]	[redacted]	[redacted]
Patients who received a non-pharmacological intervention AND took an AChEI	N/R	N/R	N/R	N/R
Patients who received a non-pharmacological intervention AND took memantine	N/R	N/R	N/R	N/R
Patients who received a non-pharmacological intervention AND took both an AChEI and memantine	N/R	N/R	N/R	N/R

Abbreviations: AChEI – acetylcholinesterase inhibitor; AD – Alzheimer's disease, N/R – not recorded.

Please complete an equivalent table for patients in Study 201 who were treated with 10 mg/kg biweekly lecanemab and with placebo.

Company response: As per Clarity AD, "non-pharmacological procedures" captured in Study 201 included any type of medical procedures that were not therapeutic medications. This consisted of procedures outside of those used to treated AD, including those as skin grafting and excision of melanoma. The type of "non-pharmacological interventions" such as cognitive training, cognitive stimulation, and reminiscence therapy were not recorded. As such, only the first three rows have been filled and we are unable to complete the final four rows of Table 37.

Table 37: Patients who received concomitant medication in Study 201, SAS

	Number of patients, n (%)			
	Lecanemab, 10 mg/kg bi-weekly (n=161)		**Placebo (n=245)**	
	MCI (n=96)	**Mild AD (n=65)**	**MCI (n=158)**	**Mild AD (n=87)**
Patients who received an AChEI	[redacted]	[redacted]	[redacted]	[redacted]
Patients who received memantine	[redacted]	[redacted]	[redacted]	[redacted]
Patients who received an AChEI AND memantine	[redacted]	[redacted]	[redacted]	[redacted]
Patients who received a non-pharmacological intervention (e.g. cognitive training, cognitive stimulation, reminiscence therapy)	N/R	N/R	N/R	N/R

Patients who received a non-pharmacological intervention AND took an AChEI	N/R	N/R	N/R	N/R
Patients who received a non-pharmacological intervention AND took memantine	N/R	N/R	N/R	N/R
Patients who received a non-pharmacological intervention AND took both an AChEI and memantine	N/R	N/R	N/R	N/R

AChEI – Acetylcholinesterase inhibitors; AD – Alzheimer's disease; MCI – mild cognitive impairment

A 17. PRIORITY QUESTION: Please provide the rationale for the choice, in the Clarity AD trial, to 'manage randomisation to ensure that approximately 70% of the total number of subjects randomized would be apolipoprotein E4 (*APOE4*) carriers'. Please provide this rationale with reference to the safety concerns identified during study 201 and subsequent required protocol amendments (as reported in the CSR for study 201):

[redacted]

[redacted]

Company response: To ensure the Clarity AD study population was consistent with prior data from Study 201 used in specified power calculations, it was required that no less than 70% of total number of subjects randomised were *APOE4* carriers. The exclusion of *APOE4* carriers in Study 201 was a requirement of an EU Health Authority in 2014. Understanding of the incidence, monitoring, and clinical management of ARIA has since improved, with the lecanemab dosing regimen being accepted by global health authorities as part of global clinical trial applications. As a result, Study 201 included 70% *APOE4* carriers and 30% *APOE4* noncarriers.

Please also indicate whether 70% is representative of the expected proportion of E4 (*APOE4*) carriers in the UK population with early stage AD.

Company response: A 2006 study by Davidson et al. reported a 63% occurrence of the *APOE4* gene among those diagnosed with AD.[6] Additionally, a 2012 systematic review pooling UK *APOE4* data from four independent studies revealed a prevalence of 56% in AD patients.[7] Furthermore, a meta-analysis focusing on the regional prevalence of *APOE4* indicated that its occurrence is notably higher in northern Europe, standing at 64.84%.[8] The studies were identified using a hand search

utilising simple search terms, including “Alzheimer’s”, “*APOE4*”, “prevalence”, and “frequency” in combination. The search engine utilised was Google Scholar.

In response to this question, UK clinical expert opinion was sought as to whether 70% *APOE4* carriers is reflective of the UK early AD population. One clinician stated it is difficult to estimate and dependent on method of ascertainment. They referred to a 2018 study by Mattsson et al reporting that approximately 66% of those with confirmed Aβ pathology are *APOE4* positive, noting that figures are likely to vary due to earlier studies not showing pathological markers in a large sample.[9] A second clinician stated the prevalence in trial populations with early AD is around 65%, as *APOE4* is not routinely tested in the UK they rely on cohort studies such as Biobank and publications for estimates. A third clinician believed that 70% was higher than might be expected in UK clinical practice, likely attributable to clinical trial recruitment methodology. They felt that considering that *APOE4* carriers have an elevated risk of developing AD, it is understandable that this group might be somewhat overrepresented in the Clarity AD study, mirroring their increased prevalence in clinical settings.[10]

Based on this feedback and the published literature, the company believes 70% is broadly representative of the proportion of APOE4 carriers expected in the early AD population in the UK.

A 18. PRIORITY QUESTION Please conduct meta-analyses, using appropriate methods as recommended by the Cochrane Handbook (e.g. inverse variance), pooling clinical efficacy data from Clarity AD with data from the subgroup of patients in Study 201 who were treated with 10 mg/kg biweekly lecanemab, for all outcomes common to both studies (CDR-SB, ADASCOMS and ADAS-Cog 14).

Company response: The inverse-variance method recommended in the Cochrane Handbook was used to pool the adjusted mean difference estimates from the mixed model for repeated measures (MMRM) in Clarity AD and Study 201, for CDR-SB, ADCOMS and ADAS-Cog14. The pooled estimate was calculated as:

$$\text{Generic inverse-variance weighted average} = \frac{\Sigma Y_i(\frac{1}{SE_i{}^2})}{\Sigma(\frac{1}{SE_i{}^2})}$$

where Y_i is the intervention effect estimated in the i^{th} study, SE_i is the standard error of that estimate, and the summation is across all studies.[11] In this analysis, only two studies were considered, Clarity AD and Study 201, so the summation was across these two studies.

The adjusted mean differences from the MMRMs used in Clarity AD and Study 201 were used for the intervention effect estimate. Standard error was calculated using the confidence intervals using the following method[11]:

$$\text{Standard error} = \frac{upper\ limit - lower\ limit}{x}$$

For 95% confidence intervals, x = 3.92, as was the case for Clarity AD, and for 90% confidence intervals, x = 3.29, as was the case for Study 201. This fixed-effect analysis is valid under the assumption that all estimates of treatment effect estimated the same underlying intervention effect. This assumption held since both Clarity AD and Study 201 investigated lecanemab 10mg/kg biweekly.

Table 38 and Table 39 show the treatment effect, confidence intervals and standard error used.

Table 38: Data from Clarity AD used in the meta-analysis – lecanemab (n=859) vs. placebo (n=875)

Outcome	Adjusted mean difference*	95% confidence interval	Standard error
CDR-SB	-0.451	-0.669, -0.233	0.111
ADCOMS	-0.05	-0.074, -0.027	0.012
ADAS-Cog14	-1.442	-2.270, -0.613	0.423

*Adjusted mean difference in change from baseline at 18 months [lecanemab – placebo]
Source: Clarity AD CSR Table 7, Table 14.2.2.2.2, Table 14.2.2.3.2;[2]
Abbreviations: AD – Alzheimer's disease; ADCOMS – Alzheimer's disease composite score; ADAS-Cog14 – Alzheimer's Disease Assessment Scale-Cognitive subscale; CDR-SB – Clinical Dementia Rating – Sum of boxes; MMRM – mixed model for repeated measures.

Table 39: Data from Study 201 used in the meta-analysis – lecanemab 10mg/kg bi-weekly (n=152) vs placebo (n=238)

Outcome	Adjusted mean difference*	90% confidence interval	Standard error
CDR-SB	-0.396	-0.821, 0.028	0.258
ADCOMS	-0.057	-0.102, -0.013	0.027
ADAS-Cog14	-2.313	-3.910, -0.717	0.971

*Adjusted mean difference in change from baseline at 18 months [lecanemab – placebo]
Source: Study 201 CSR Table 14.2.1.5a, Table 14.2.1.5b, Table 14.2.1.5d.[1]
Abbreviations: AD – Alzheimer's disease; ADCOMS – Alzheimer's disease composite score; ADAS-Cog14 – Alzheimer's Disease Assessment Scale-Cognitive subscale; CDR-SB – Clinical Dementia Rating – Sum of boxes; MMRM – mixed model for repeated measures.

All analyses were conducted using Microsoft Excel®. Table 40 shows the pooled estimates of adjusted mean difference for CDR-SB, ADCOMS, and ADAS-Cog14. Lecanemab 10 mg/kg biweekly showed a benefit compared to placebo across all three common outcomes, which was consistent with the benefit observed in Clarity AD.

Table 40: Meta-analyses of common outcomes between Clarity AD and Study 201 (lecanemab 10mg/kg biweekly vs placebo)

Outcome	Adjusted mean difference *
CDR-SB	-0.442
ADCOMS	-0.051
ADAS-Cog14	-1.581

*Adjusted mean difference in change from baseline at 18 months [lecanemab – placebo]
Abbreviations: AD – Alzheimer's disease; ADCOMS – Alzheimer's disease composite score; ADAS-Cog14 – Alzheimer's Disease Assessment Scale-Cognitive subscale; CDR-SB – Clinical Dementia Rating – Sum of boxes.

A 19. The CS (Section B.2.3.1) describes Clarity AD as 'conducted across 14 countries including eight sites in the UK.' However, the subject disposition tables in the CSR for Clarity AD (Table 14.1.1.2.1) suggest that only 48 UK patients were included in the study. Please confirm the total number of UK participants in Clarity AD.

Company response: Table 14.1.1.2.1 of the CSR is correct, 48 UK patients were included in the study. There were 24 UK patients in each of the MCI due to AD and mild AD subgroups.

Adverse events

A 20. PRIORITY QUESTION Please provide a breakdown of TESAEs by type, in particular ARIA-E and ARIA-H, using MedDRA preferred terms.

Company response: Table 41 presents a breakdown of TESAEs by MedDRA system organ class and preferred term for the safety analysis set (SAS) in Clarity AD. ARIA is categorised under nervous system disorders and more specifically ARIA-E is described by the preferred term amyloid related imaging abnormality-edema/effusion. There are multiple preferred terms for ARIA-H dependent on how it presents in the patient. The preferred terms used to describe the TESAEs of ARIA-H occurring in Clarity AD were amyloid related imaging abnormality-microhaemorrhages and haemosiderin deposits, cerebral haemorrhage and haemorrhage intracranial.

Table 41: Treatment-emergent serious adverse events by system organ class and preferred term (SAS)

MedDRA system organ class preferred term	Number of patients, n (%)	
	Lecanemab (N=898)	Placebo (N=897)
Subjects with any treatment-emergent serious adverse event	126 (14.0)	101 (11.3)
Nervous system disorders	[redacted]	[redacted]
Amyloid related imaging abnormality-microhaemorrhages and haemosiderin deposits	[redacted]	[redacted]
Amyloid related imaging abnormality-oedema/effusion	[redacted]	[redacted]
Cerebral haemorrhage	[redacted]	[redacted]
Haemorrhage intracranial	[redacted]	[redacted]
Blood and lymphatic system disorders	[redacted]	[redacted]
Cardiac disorders	[redacted]	[redacted]
Ear and labyrinth disorders	[redacted]	[redacted]
Eye disorders	[redacted]	[redacted]
Gastrointestinal disorders	[redacted]	[redacted]
General disorders and administration site conditions	[redacted]	[redacted]
Hepatobiliary disorders	[redacted]	[redacted]
Immune system disorders	[redacted]	[redacted]
Infections and infestations	[redacted]	[redacted]
Injury, poisoning and procedural complications	[redacted]	[redacted]
Investigations	[redacted]	[redacted]
Metabolism and nutrition disorders	[redacted]	[redacted]
Musculoskeletal and connective tissue disorders	[redacted]	[redacted]
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	[redacted]	[redacted]
Product issues	[redacted]	[redacted]
Psychiatric disorders	[redacted]	[redacted]
Renal and urinary disorders	[redacted]	[redacted]
Reproductive system and breast disorders	[redacted]	[redacted]
Respiratory, thoracic and mediastinal disorders	[redacted]	[redacted]
Skin and subcutaneous tissue disorders	[redacted]	[redacted]
Social circumstances	[redacted]	[redacted]
Vascular disorders	[redacted]	[redacted]

Source: Clarity AD CSR[2], Table 18 and Table 14.3.2.2.1
Abbreviations: MedDRA – Medical Dictionary for Regulatory Activities; SAS – Safety Analysis Set

A 21. Please provide any safety data that are available from the OLE or confirm that no safety data are yet available from this study.

Company response: Safety data from the OLE are available for 1,612 patients at the interim data cut off on 1st December 2022. This Safety Analysis Set consists of [redacted] treated with lecanemab in the core study, and [redacted] treated with placebo in the core study who then crossed over to lecanemab in the OLE. Patients who received placebo in the core study and did not enter the OLE are not included. Safety data are

only reported for the entire Safety Analysis Set, hence are not stratified according to treatment arm allocation in the core study.

Extent of exposure

Duration of exposure to treatment was calculated in the same manner as in the core study (see Section B.2.10.1 Extent of exposure). The mean duration of exposure to lecanemab in the OLE was [redacted] months (range: [redacted]) (Table 42). Overall, [redacted] patients had exposure of ≥12 months and [redacted] patients had exposure of ≥24 months, and [redacted] patients had exposure of greater than or equal to 36 months.

Table 42: Clarity AD OLE drug exposure

Duration of exposure (months)	Lecanemab (n=1,612)
n	[redacted]
Mean (SD)	[redacted]
Min, Max	[redacted]
Total duration (subject-years)[a]	[redacted]

Source: Table 14.3.1.1.1, Clarity AD OLE synoptic CSR[12]
Abbreviations: Max – maximum; Min – minimum; n – number of subjects in treatment group; OLE – open-label extension; SD – standard deviation.
[a] Total duration (subject-years) – summation over all subjects' exposure durations.

AEs overview

A summary of TEAEs that occurred in the OLE is presented in Table 43. Of the 1,612 subjects in the OLE Safety Analysis Set, [redacted]) had at least one TEAE, the majority of which were mild or moderate and nonserious. This was lower compared to lecanemab ([redacted]) in the core study but greater than placebo ([redacted]) in the core study. Severe TEAEs were reported for [redacted]) patients. Infusion-related reactions were mild to moderate and could be managed with prophylactic treatment.

As stated above, data for OLE patients separated by patients who received placebo in the core study and patients who received lecanemab in the core study was not available. Therefore, it was not possible to determine whether the subsequent infusion-related reactions in the OLE were in patients who crossed over from placebo (i.e., patients receiving their first dose of lecanemab) or in patients already being treated with lecanemab.

Of the 1,612 subjects in the OLE Safety Analysis Set, [redacted] patients had treatment-emergent serious adverse events (TESAEs). TEAEs leading to study drug dose interruption and study drug withdrawal were reported for [redacted] and [redacted] patients, respectively. TEAEs of special interest (ARIA-E, ARIA-H [cerebral microhaemorrhages, superficial siderosis, macrohaemorrhage], infusion-related reactions, skin rash, other hypersensitivity, suicidal ideation, and suicidal behaviour) were reported for [redacted] subjects.

Table 43: Overview of TEAEs – Lecanemab treated period (Clarity AD OLE, SAS)

Category	Lecanemab (N=1612), n (%)
TEAEs	[redacted]
Treatment-related TEAEs[a]	[redacted]
Severe TEAEs	[redacted]
Serious TEAEs	[redacted]
Deaths[b]	[redacted]
Other SAEs[c]	[redacted]
Life threatening	[redacted]
Requires inpatient hospitalization or prolongation of existing hospitalisation	[redacted]
Persistent or significant disability or incapacity	[redacted]
Congenital anomaly/birth defect	[redacted]
Important medical events	[redacted]
TEAEs leading to study drug dose adjustment	[redacted]
TEAEs leading to study drug withdrawal	[redacted]
TEAEs leading to study drug dose interruption	[redacted]
TEAEs leading to infusion interruption	[redacted]
TEAEs of special interest	[redacted]

Source: Clarity AD OLE, Table 5[13]
Abbreviations: OLE – Open-label extension; SAE – Serious adverse event; SAS – Safety analysis set; TEAE – Treatment emergent adverse event
a: Includes TEAEs considered by the Investigator to be related to study drug or TEAEs with missing causality.
b: Includes all subjects with SAE resulting in death.
c: Includes subjects with nonfatal SAEs only. If a subject had both fatal and nonfatal SAEs, the subject is counted in the fatal row and is not counted in the nonfatal row.

TEAEs of any severity occurring in ≥5% of patients in either treatment arm (this includes any TEAE that occurred in more than one patient and includes infusion-related reactions and ARIA) reported during the OLE are summarised by decreasing frequency in Table 44. The most common events overall were infusion related reactions ([redacted]), ARIA-H cerebral microhaemorrhage ([redacted]), COVID-19 ([redacted]), and ARIA-E ([redacted]), which is consistent with the core study. TEAEs of infusion-related reactions and ARIA-E occurred at a lower rate in the OLE compared

to lecanemab in the core study. Excluding infusion-related reactions and ARIA, TEAEs occurring in ≥5% of subjects were lower in the OLE compared to lecanemab in the core study.

Table 44: Treatment-emergent AEs reported in ≥5% of patients (Clarity AD OLE, SAS)

MedDRA Preferred Term	Lecanemab (N=1,612), n (%)
Subjects with any TEAE	[redacted]
Infusion related reaction	[redacted]
Amyloid related imaging abnormality-microhaemorrhages and haemosiderin deposits	[redacted]
COVID-19	[redacted]
Amyloid related imaging abnormality-oedema/effusion	[redacted]
Headache	[redacted]
Fall	[redacted]
Urinary tract infection	[redacted]
Back pain	[redacted]
Superficial siderosis of central nervous system	[redacted]
Arthralgia	[redacted]
Dizziness	[redacted]

Source: Clarity AD OLE, Table 6[13]
Abbreviations: AE – adverse event; MedDRA – Medical Dictionary for Regulatory Activities; OLE – Open-label extension; SAS – Safety analysis set; TEAE – treatment-emergent adverse event

Adverse events of special interest

Incidence of AESIs such as infusion-related reactions, skin rash, other hypersensitivity reactions, ARIA-E, and ARIA-H in the OLE Safety Analysis Set was similar to incidence in the lecanemab arm in the core study ([redacted] vs. [redacted], respectively) (Table 45).

Table 45: Treatment-emergent adverse events of special interest (Clarity AD OLE, safety population)

Preferred term	Lecanemab (n=1,612) n (%)
Subjects with any TEAE of special interest	[redacted]
ARIA-E	[redacted]
ARIA-H	[redacted]
Macrohaemorrhage	[redacted]
Superficial siderosis	[redacted]
Cerebral microhaemorrhage	[redacted]
Infusion-related reactions	[redacted]
Skin rash	[redacted]
Other hypersensitivity	[redacted]
Suicidal behaviour	[redacted]
Suicidal ideation	[redacted]

Source: Table 8, Clarity AD OLE synoptic CSR[12]
Abbreviations: ARIA-E – amyloid-related imaging abnormality-oedema/effusion; ARIA-H – amyloid-related imaging abnormality-microhaemorrhage and haemosiderin deposit; n – number of subjects in treatment group; OLE – open-label extension; TEAE – treatment-emergent adverse events.

Deaths

There were 15 treatment-emergent deaths reported in Clarity AD, of which six occurred in the Core Study with lecanemab treatment and nine additional deaths in the OLE. AEs leading to death in the extension phase were myocardial infarction, COVID-19 pneumonia, COVID-19, cerebral haemorrhage, possible seizure and cerebrovascular accident, acute multifocal intracerebral haemorrhage post tissue plasminogen activator, road traffic accident, and cardiac failure acute.

A 22. PRIOITY QUESTION Please provide details of the MRI safety monitoring regimen applied during the Clarity AD trial. Please describe the rationale for the MRI safety monitoring regimen specified for the Clarity AD trial, with reference to the [redacted]. Did the MRI safety monitoring regimen vary according to geographic location (specifically, between European and other locations)? Please also provide details of any deviations from the specified number or timing of MRI scans that occurred during the COVID-19 pandemic.

Company response: The appropriate MRI monitoring schedule for Clarity AD was determined based on the frequency, timing, and severity of ARIA observed in Study 201. In Study 201, MRI monitoring took place at Week 9, Week 13, Month 6, Month 9, Month 12, Month 15, and Month 18. In Clarity AD, MRI monitoring took place at Week 9, Week 13, Month 6, Month 12, and Month 18. There were no differences in the MRI safety monitoring regimen across geographic locations.

There were [redacted]) of missed study visits related to COVID-19 in Clarity AD. Of these, [redacted]) were scheduled visits for safety MRI assessments. In addition, there were [redacted]) of missed safety MRI assessments related to COVID-19. Overall, approximately [redacted]) had protocol deviations related to safety MRI.

A 23. PRIORITY QUESTION With reference to the recommendations (appendix C.1.4.2 of the CS)

[redacted]**,**

please provide details of:

a) The numbers patients, in the Clarity AD study, who met the criteria for dose suspension specified in these recommendations.

Company response: [redacted] ([redacted]%) patients in the lecanemab arm and [redacted] ([redacted]%) patients in the placebo arm in Clarity AD met the criteria for dose suspension specified in these recommendations. Details of patients requiring dose suspensions in Clarity AD relating to responses to parts a)-f) of this question are presented in Table 46.

b)The number patients, in the Clarity AD study, in whom treatment was suspended due to ARIA.

Company response: Of those patients, [redacted] ([redacted]%) patients in the lecanemab arm and [redacted] ([redacted]%) in the placebo arm had their treatment suspended due to ARIA (Table 46).

c) The number of patients who experienced more than one suspension of treatment, due to ARIA, during the Clarity AD study.

Company response: Of those patients, [redacted] ([redacted]%) in the lecanemab arm and [redacted] ([redacted]%) in the placebo arm experienced more than one suspension of treatment due to ARIA (Table 46).

d) The mean, SD and range of the duration of treatment suspensions due to ARIA experienced by patients in the Clarity AD study.

Company response: Mean duration of treatment suspension due to ARIA was [redacted] weeks (SD [range]: [redacted] [[redacted]]) in the lecanemab arm and [redacted] weeks (SD [range]: [redacted] [[redacted]]) in the placebo arm (Table 46).

e) The numbers of additional MRI scans and clinical assessments undertaken in patients, in the Clarity AD study, in whom treatment had been suspended due to ARIA.

Company response: For patients whose treatment was suspended due to ARIA (Table 46), the mean number of additional MRI scans required was [redacted] (SD: [redacted]) in the lecanemab arm and [redacted] (SD: [redacted]) in the placebo arm.

f) The number of patients, in the Clarity AD study, in whom dosing was not resumed after suspension and additional monitoring.

Company response: [redacted] ([redacted]%) and [redacted] ([redacted]%) patients in the lecanemab and placebo arms, respectively, did not resume dosing following suspension and additional monitoring due to ARIA (Table 46).

Table 46: Dose suspension due to ARIA events in Clarity AD Core study, SAS

	Lecanemab (n=898) n (%)	**Placebo (n=897) n (%)**	**Total (n=1795) n (%)**
Subjects who met the criteria for dose suspension specified in the draft SmPC[a]	[redacted]	[redacted]	[redacted]
Subjects in whom treatment was suspended due to ARIA[b,c]	[redacted]	[redacted]	[redacted]
Subjects who experienced more than one suspension of treatment due to ARIA[d,e]	[redacted]	[redacted]	[redacted]
Duration of treatment suspensions due to ARIA[f] (weeks)			
Mean (SD)	[redacted]	[redacted]	[redacted]
Range[g]	[redacted]	[redacted]	[redacted]
Number of additional MRI scans in whom treatment had been suspended due to ARI			

Mean (SD)	[redacted]	[redacted]	[redacted]
Range[h]	[redacted]	[redacted]	[redacted]
Subjects in whom dosing was not resumed after suspension and additional monitoring[e]	[redacted]	[redacted]	[redacted]

Abbreviations: TE = treatment-emergent, ARIA-E = amyloid-related imaging abnormality-edema/effusion, ARIA-H = amyloid-related imaging abnormality-hemorrhage, MH = microhemorrhage, SS = superficial siderosis.
a: TE symptomatic ARIA-E with moderate or severe in clinical severity or in radiographic severity, TE asymptomatic ARIA-E with moderate or severe in radiographic severity, TE symptomatic ARIA-H (MH, SS), or TE asymptomatic ARIA-H (MH, SS) with moderate or severe in radiographic severity.
b: Included both study treatment interruption and study treatment discontinuation. Any missed doses after ARIA led to study treatment interruption and study treatment discontinuation and until resumption of treatment are considered as suspension of treatment due to ARIA.
c: Percentage is based on # of subjects who met the criteria for dose suspension specified in the draft SmPC.
d: Counted if subject had second or more suspension of treatment after resumption of treatment.
e: Percentage is based on # of subjects in whom treatment was suspended due to ARIA
f: Missed doses are counted by last scheduled visit. Duration is calculated using the number of missed doses x 2 weeks. Total duration is used if subjects had more than one suspension of treatment due to ARIA.
g: [redacted] subjects ([redacted]) had no scheduled visit where subject could have treatment after ARIA, which shows 0 in duration of treatment suspension.
h: [redacted] subjects ([redacted]) had no additional MRI scans because ARIA-E resolved one month after onset and scheduled visit MRI could cover follow up MRI, which shows 0 in number of additional MRI scans.

g) How and to what extent are treatment suspension and additional monitoring are reflected in the economic model?

Company response: As detailed in the CS, Document B, Section B.3.5.2, mean compliance ([redacted]) for lecanemab was included in the model, informed by Clarity AD. This was defined as (total number of infusions patients actually received) / (total number of infusions the patients could have received), regardless of infusion interruption.[14] As such, treatment suspension due to ARIA would be captured within compliance, and therefore reflected in the treatment acquisition and administration costs in the model.

Additionally, as detailed in Section B.3.5.5, UK clinical expert opinion was sought to inform management of ARIA events thus informing AE management costs in the model. Based on the clinicians' feedback, management of ARIA was not expected to differ between ARIA-E and ARIA-H. For mild-moderate ARIA events, clinical assessment and two additional MRI scans would be required. For severe-serious ARIA events, management included four additional MRI scans alongside clinical assessment and hospitalisation. The cost of this additional monitoring and the duration, where relevant, is reflected in AE management costs in the model.

Section B: Clarification on cost-effectiveness data

Updated company base case

Alongside the responses to the clarification questions, the company have submitted an updated economic model with the following updates applied to the base case:

1) Updated transition probabilities from Potashman et al. (2021)[15]

In the original company submission, transition probabilities were taken from Potashman et al, as reported by Herring et al.[15,16] The updated company model uses transition probabilities as reported by Potashman et al. directly (Table 47) for the following reasons:

- The transition probabilities reported by Herring et al. calculated an AD 'landing spot' distribution for patients leaving the MCI due to AD health state, requiring an additional calculation step.[16] This is not necessary when using the data reported directly from Potashman et al.[15]

- The updated transitions more closely align with the source data as Potashman et al., reported transition probabilities to a greater level of precision than presented by Herring et al.[15,16]

Table 47: Transition probabilities reported by Potashman et al.

	To					
From	**Asymptomatic**	**MCI-AD**	**Mild AD**	**Moderate AD**	**Severe AD**	**Died**
Asymptomatic	59.2%	40.8%	0.0%	0.0%	0.0%	0.0%
MCI-AD	5.3%	68.2%	15.9%	5.7%	0.2%	4.7%
Mild AD	0.0%	3.0%	51.8%	31.6%	4.3%	9.2%
Moderate AD	0.0%	0.0%	1.8%	38.4%	28.6%	31.2%
Severe AD	0.0%	0.0%	0.0%	1.3%	52.0%	46.7%

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

The transition probability matrix in Table 47 was adjusted for use in the model by removing transitions to the Asymptomatic and Died health states. Transitions to the asymptomatic health state were added to the probability of moving to, or remaining in, the MCI-AD state, reflecting the methodology used in Herring et al. The remaining probabilities were re-weighted across transitions to alive health states to create the matrix for use in the model (Table 48), as the probability of death is applied using

adjusted general population life tables. The updated transition probability matrix is consistent with the transition probability matrix used in the original company submission (Table 49), with no transition probability changing by more than 0.7% compared with the original matrix. More detail on the transformation from annual to monthly cycle lengths is provided in the response to B8.

Table 48: Transition probabilities used in the model (Potashman et al., with death and asymptomatic health state transitions removed)

	To			
From	**MCI-AD**	**Mild AD**	**Moderate AD**	**Severe AD**
MCI-AD	77.1%	16.7%	6.0%	0.2%
Mild AD	3.3%	57.1%	34.8%	4.7%
Moderate AD	0.0%	2.6%	55.8%	41.6%
Severe AD	0.0%	0.0%	2.4%	97.6%

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

Table 49: Transition probabilities used in the model (original company submission)

	To			
From	**MCI-AD**	**Mild AD**	**Moderate AD**	**Severe AD**
MCI-AD	76.8%	16.8%	6.3%	0.0%
Mild AD	3.3%	57.1%	35.2%	4.4%
Moderate AD	0.0%	2.9%	55.1%	42.0%
Severe AD	0.0%	0.0%	1.9%	98.1%

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

Using the updated transition probability matrix decreases the ICER by £[redacted] to £[redacted] compared with the original base case.

2) Updated Clarity-AD patient counts at end of core study (81 weeks)

The original company submission used 79-week patient count data from Clarity-AD to inform transitions from 0-18 months. However, some patients did not complete their last visit until 81 weeks. Therefore, the updated economic model uses the 81-week patient count data for health states using CDR-SB and global CDR (scenario analysis only) as presented in Table 50 and Table 51, respectively. These data more accurately reflect the ITT FAS+ sample sizes (lecanemab, N=[redacted]; placebo, N=[redacted] at week 81, vs. lecanemab, N=[redacted]; placebo, N=[redacted] at week 79), as some patients attended their final visit more than one week later than was outlined in the protocol.

Table 50: Clarity AD, Summary of Counts for Subjects in Each Health State Using CDR-SB, Core Study, week 81 data (end of core study)

Baseline state	MCI due to AD n (%)	Mild AD n (%)	Moderate AD n (%)	Severe AD n (%)
Lecanemab				
Placebo				

Abbreviations: AD, Alzheimer's disease; FAS, full analysis set; ITT, intention-to-treat; MCI, mild cognitive impairment.

Table 51: Clarity AD, Summary of Counts for Subjects in Each Health State Using global CDR, Core Study, week 81 data (end of core study)

Baseline state	MCI due to AD n (%)	Mild AD n (%)	Moderate AD n (%)	Severe AD n (%)
Lecanemab				
Placebo				

Abbreviations: AD, Alzheimer's disease; FAS, full analysis set; ITT, intention-to-treat; MCI, mild cognitive impairment

Using the updated Clarity-AD patient count data increases the ICER by £[redacted], [redacted] to £[redacted] compared with the original base case.

3) Corrected Alzheimer's Society health state costs

The updated economic model uses corrected inputs for direct medical and direct non-medical health state costs (community and institution) from the Alzheimer's Society report.[17] Costs were inflated from 2013 prices using the PSSRU inflation indices.[18] The costs were previously included correctly in the 'Cost Calculations' sheet, however were not carried through correctly to the model input sheet. Using the updated health state costs decreases the ICER by £[redacted], ([redacted]) to £[redacted] compared with the original base case.

Table 52: Direct medical and direct non-medical costs, community, and institution

Health state	Direct medical		Direct non-medical	
	Community	Institution	Community	Institution
MCI-AD	£2,704.75	£4,428.28	£1,949.42	£28,613.11
Mild AD	£3,182.06	£5,209.74	£3,610.04	£28,613.11
Moderate AD	£3,117.29	£10,916.87	£8,989.82	£29,744.36
Severe AD	£13,022.05	£10,050.50	£11,938.23	£29,928.27

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

[redacted].

Updated company base case – cost-effectiveness results

The updated base case results are presented in Table 53. Model results are presented for both list price and [redacted].

Table 53: Updated base case results (list and PAS price)

Technology	Total			Incremental			ICER (list price)	ICER (PAS price)
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs		
Updated transition matrix								
SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lecanemab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
+ Updated Clarity AD patient count data								
SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lecanemab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
+ Correct MRU costs								
SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lecanemab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Updated base case								
SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lecanemab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Clarification scenario analyses – cost-effectiveness results

An overview of scenario analyses results is presented in Table 54. The results are discussed in further detail in response to the respective questions.

Table 54: Summary of scenario analysis results

Question	Scenario	Incremental Costs	Incremental QALYs	ICER	ICER including PAS	% difference vs base case ICER (inc. PAS)
Updated company base case		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
B2	*APOE4* non-carrier subgroup	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
B2	*APOE4* homozygotes subgroup	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
B2	*APOE4* heterozygotes subgroup	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
B8 (g)	Clarity-AD patient counts – worst case imputation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
B8 (h)	Clarity-AD data for full time horizon	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
B8 (h)	Clarity-AD data for full time horizon – exploratory scenario using Weibull for transitions 1-3 and exponential for transition 4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
B9 (f)	Rate of death as per Potashman et al (2021)[15]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
B10	Potashman et al (2021) alternate transition matrix calculation.	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
B14 (b)	HR=1 for mortality in MCI due to AD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
B15 (b)	AE disutility (moderate and severe AEs only)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
B15 (b)	AE disutility (all AEs)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
B17 (b)	Gen. pop utility cap	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
B17 (f)	Treatment-independent utilities for MCI and mild AD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
B19 (b)	Patient reported at moderate and proxy at severe	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
B20 (a)	Diagnostic testing	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
B22 (b)	Symptomatic treatment from Lenox-Smith	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
B22 (d)	Symptomatic treatment, none in MCI and no memantine in mild AD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
B22 (b)	+25% cost of symptomatic treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
B22 (b)	-25% cost of symptomatic treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
B23 (d)	100% compliance	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
B24	Health state costs reduced by 10%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

General

B 1. A comprehensive overview of model input parameters is lacking in the CS (Table 64 in the CS does not provide this clearly). Please provide an overview of all model input parameters (including standard error/confidence intervals) and their sources.

Company response: Please refer to the 'Control' sheet of the model for a comprehensive overview of model inputs parameters and their respective standard errors/confidence intervals. A summary of model inputs parameters was included in the CS as a pragmatic approach, as a table including all model parameters would amount to approximately 530 rows of data.

Population

B 2. The scope mentions the subgroup based on apolipoprotein E 4 (*APOE4*) gene carrier status. Please provide subgroup analyses for subgroups defined by *APOE4*, as well as an updated version of the economic model.

Company response: Please refer to the response to Question A9.

B 3. According to the CS in Clarity AD, Lecanemab is used alongside AChEIs and non-pharmacological interventions. Please elaborate with supporting evidence that this is consistent with UK clinical practice.

Company response: Further UK clinical expert validation was sought to inform this response. All three experts stated that lecanemab would be used alongside AChEIs and non-pharmacological interventions in the UK for patients with mild AD.[10]

For MCI due to AD, there were mixed responses regarding use of AChEIs. One expert stated that AChEIs are given to patients with MCI due to AD in many centres as there is some evidence that they have greater benefit earlier, and this is likely to continue alongside DMTs. Another stated AChEIs would be used less frequently relative to mild AD patients, allowing for variations in clinical practice across regions and individuals. The third expert stated AChEIs should not be used for MCI due to AD.

Based on this clinical expert feedback, the company believes that while there is some uncertainty regarding use of AChEIs, it is reasonable to assume a proportion of patients with MCI due to AD would receive these alongside non-pharmacological interventions, hence Clarity AD is consistent with UK clinical practice in this regard.

B 4. According to the CS, the comparator consists of symptomatic treatment only, reflected in CS Table 52.

a) Please clarify the evidence and methods used to obtain the distribution in CS Table 52.

Company response: The company would like to clarify that as per the final scope for this appraisal, the comparator in the CS consists of non-pharmacological and pharmacological treatment, the latter including symptomatic treatment. As discussed in the CS, Document B, Section B.3.1, non-pharmacological interventions (e.g., cognitive stimulation therapy, group reminiscence therapy, cognitive rehabilitation/occupational therapy, etc.) are not explicitly considered within this analysis for either treatment arm. The outcomes for these interventions are expected to be captured indirectly through health state costs and utility, and their use is expected to be equal in both treatment groups.

The methods used to obtain the distribution in CS Table 52 are as follows. For each CDR-SB or global CDR observation, patients in the ITT FAS+ population were classified into one of the four health states (MCI due to AD, mild AD, moderate AD and severe AD). Patients were assumed to remain in that state until the next observation, death, or study withdrawal. Health state definitions are further described in CS Table 3.

To ensure the quantities of symptomatic treatments reflected the duration of time spent in each health state, total time in each health state was calculated by summing time in each health state across all patients. Total time receiving symptomatic treatment was calculated by summing time in receipt of each symptomatic treatment whilst in each health state across all patients. The proportion of time for which symptomatic treatment was received of total time spent by patients in each health state was calculated by dividing patients in each health state by the total time for each treatment.

b) Please elaborate whether the comparator, symptomatic treatment only as reflected in CS Table 52, is consistent with the ITT population from Clarity AD.

Company response: As explained in the methods in B16a above, the symptomatic AD treatment distributions presented in CS Table 52 is based on data from the ITT (FAS+) population from Clarity AD.

c) Please justify with appropriate evidence that the comparator, symptomatic treatment only as reflected in CS Table 52, is consistent with UK clinical practice.

Company response: To respond to this question, UK clinical expert opinion was sought on the use of symptomatic treatments in UK clinical practice, specifically regarding the proportions of AChEI and memantine use in each AD health state.

In summary, two of the three clinicians stated that clinical trial populations are not fully reflective of wider clinical practice, and one stated they expect a lower proportion of patients with MCI due to AD to be treated with an AChEI (closer to 25% of patients). For mild AD onwards, the same clinician believed the proportions of AChEI treatment observed in Clarity AD to be reasonable, however noted that memantine is used far less in UK clinical practice than AChEI, aligning with the proportions seen in Clarity AD, with actual use being closer to 10%, dependent on region and individual clinicians.[10] The third clinician stated giving symptomatic therapies (AChEIs) outside of NICE guidelines is likely to be variable across the UK, potentially being given earlier more in neurology centres. On average, they would expect AChEI use to increase from MCI due to AD to mild AD to moderate AD but expect the use in severe AD to be lower. Two clinicians stated they would not expect use of memantine in MCI due to AD and one would also not expect this in mild AD is not their practice, however would expect around 40% in moderate AD, then reducing in severe AD.[10]

Based on this clinical expert feedback, it is possible that lower proportions of AChEIs and memantine would be used in MCI due to AD in UK clinical practice compared to CS Table 52. However, there is some variability of opinions for the figures for mild AD onwards, which the company believes is reflective of the varied clinical practice of prescribing symptomatic AD medications in the UK.

Model structure

B 5. PRIORITY QUESTION According to a recent publication (International Pharmaco-Economic Collaboration on Alzheimer's Disease (IPECAD) modelling challenge) comparing cost-effectiveness models for Alzheimer's disease and related dementia's (Handels et al., 2022 https://doi.org/10.1002/alz.12811; Table 3), the MMSE is mostly used to define health states (i.e. disease severity). Nevertheless, the CS model structure uses CDR-SB for this purpose, to align with the primary endpoint of Clarity AD. Moreover, the health state utility values and costs were informed using data categorised based on the MMSE.

a) Please provide the CDR-SB threshold values used to define MCI due to AD, mild AD, moderate AD, and severe AD and provide justification for using these threshold values.

Company response: The CDR-SB thresholds used to define model health states are presented in Table 55, as defined in the CS, Document B, Section B.1.3.2. The thresholds used are sourced from O'Bryant et al. (2008), a study to evaluate staging of CDR-SB compared with Global CDR score thus providing interpretive guidelines for CDR-SB scores.[19]

Table 55: CDR-SB dementia staging scores

Clinical disease stage	CDR-SB
MCI due to AD	0.5-4.0
Mild dementia due to AD	4.5-9.0
Moderate dementia due to AD	9.5-15.5
Severe dementia due to AD	16.0-18.0

Source: O'Bryant et al.[19]
Abbreviations: AD – Alzheimer's disease; MCI – Mild cognitive impairment; CDR – Clinical Dementia Rating; CDR-SB – Clinical Dementia Rating Sum of Boxes

b) Please provide further justification for deviating from common modelling practices by using CDR-SB to define health states (instead of MMSE).

Company response: CDR-SB was chosen to define model health states in favour of MMSE, given that CDR-SB has been demonstrated to adequately detect slowing of progression with manageable sample sizes in the early AD patient population, whilst

MMSE has not.[2,20] Furthermore, CDR-SB assesses both cognition and function, while MMSE is designed to assess cognition only.

In Section 8.2.2 of the EMA scientific guideline for the clinical investigation of medicines for the treatment of Alzheimer's disease, it states that cognitive instruments, such as Mini-Mental State Examination (MMSE), the Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS-Cog), and neuropsychological test items show relatively little change over time in prodromal AD or MCI due to AD patients, primarily due to ceiling effects in many of the items that make up these scales.[21,22] It also states both cognition and function should be assessed through the primary endpoint for patients with prodromal AD or MCI due to AD.

Whilst the company acknowledges that some published economic models of treatments for AD have utilised MMSE to define health states, these models typically evaluated symptomatic treatments in patients with mild to moderate dementia due to AD. Out of the 19 UK-specific economic modelling studies identified in the SLR, only one study included MCI at baseline.[23] However, this study evaluated cost-effectiveness of screening tests, and therefore, the measure used to define health states in this study is not relevant. The rest focused on mild or more severe AD patients, and all except for Guo et al. 2014 assessed for the cost-effectiveness of symptomatic treatments (AChEIs and memantine).[24] While the model developed by Guo et al. simulated for the cost-effectiveness of a hypothetical disease modifying treatment, their base-case analysis focused on a patient population with a more progressed disease than the target treatment patient population for lecanemab, given the patient profile was generated from donepezil clinical trials (ie, mild to moderate dementia due to AD). MMSE may have been a suitable measure to define health states in patients with mild or more severe AD, but not in patients with early AD.

The economic model submitted for lecanemab is consistent with published clinical and economic models of DMTs for AD, which have defined health states using CDR-SB. Of the models presented by Handels et al., summarising the results of the IPECAD workshop, five of nine economic models defined treatment effects for disease modifying therapies using CDR-SB;[16,25–28] four of these studies defined health states or disease progression, wholly or in part, using CDR-SB.[16,26–28] In

addition, CDR-SB has been used to define health states in the economic evaluation of lecanemab performed by the Institute for Clinical and Economic Review (ICER), and to define health states in a simulation of outcomes for lecanemab reported by Monfared et al.[29,30]

c) Please provide an overview of the baseline, 3, 6, 9, 12, 15, and 18 months health state occupancy (both % and N) based on Clarity AD, using i) the MMSE and ii) CDR-SB to define health states.

Company response: Health state occupancy per visit based on CDR-SB is presented in Table 56. While MMSE data are available from Clarity AD, for the reasons outlined in response to part b) it is an inappropriate measure for definition of health states and AD progression for DMTs. Therefore, health state occupancy data using MMSE have not been provided.

Table 56: Summary of Counts for Subjects in Each Health State Using CDR-SB Score by Visit

Visit	Baseline State	State at Corresponding Visit	Placebo n (%)	Lecanemab 10mg/kg Biweekly n (%)
Week 13	MCI due to AD (placebo: N=672, lecanemab: N=649)	MCI due to AD	[redacted]	[redacted]
		Mild AD	[redacted]	[redacted]
		Moderate AD	[redacted]	[redacted]
		Severe AD	[redacted]	[redacted]
		Death	[redacted]	[redacted]
	Mild AD (placebo: N=177, lecanemab: N=175)	MCI due to AD	[redacted]	[redacted]
		Mild AD	[redacted]	[redacted]
		Moderate AD	[redacted]	[redacted]
		Severe AD	[redacted]	[redacted]
		Death	[redacted]	[redacted]
	MCI due to AD or Mild AD (placebo: N=849, lecanemab: N=824)	MCI due to AD	[redacted]	[redacted]
		Mild AD	[redacted]	[redacted]
		Moderate AD	[redacted]	[redacted]
		Severe AD	[redacted]	[redacted]
		Death	[redacted]	[redacted]
Week 27	MCI due to AD (placebo: N=663, lecanemab: N=633)	MCI due to AD	[redacted]	[redacted]
		Mild AD	[redacted]	[redacted]
		Moderate AD	[redacted]	[redacted]
		Severe AD	[redacted]	[redacted]
		Death	[redacted]	[redacted]

Visit	Baseline State	State at Corresponding Visit	Placebo n (%)	Lecanemab 10mg/kg Biweekly n (%)
	Mild AD (placebo: N=165, lecanemab: N=165)	MCI due to AD	[redacted]	[redacted]
		Mild AD	[redacted]	[redacted]
		Moderate AD	[redacted]	[redacted]
		Severe AD	[redacted]	[redacted]
		Death	[redacted]	[redacted]
	MCI due to AD or Mild AD (placebo: N=828, lecanemab: N=798)	MCI due to AD	[redacted]	[redacted]
		Mild AD	[redacted]	[redacted]
		Moderate AD	[redacted]	[redacted]
		Severe AD	[redacted]	[redacted]
		Death	[redacted]	[redacted]
Week 39	MCI due to AD (placebo: N=654, lecanemab: N=623)	MCI due to AD	[redacted]	[redacted]
		Mild AD	[redacted]	[redacted]
		Moderate AD	[redacted]	[redacted]
		Severe AD	[redacted]	[redacted]
		Death	[redacted]	[redacted]
	Mild AD (placebo: N=159, lecanemab: N=158)	MCI due to AD	[redacted]	[redacted]
		Mild AD	[redacted]	[redacted]
		Moderate AD	[redacted]	[redacted]
		Severe AD	[redacted]	[redacted]
		Death	[redacted]	[redacted]
	MCI due to AD or Mild AD (placebo: N=813, lecanemab: N=781)	MCI due to AD	[redacted]	[redacted]
		Mild AD	[redacted]	[redacted]
		Moderate AD	[redacted]	[redacted]
		Severe AD	[redacted]	[redacted]
		Death	[redacted]	[redacted]
Week 53	MCI due to AD (placebo: N=635, lecanemab: N=612)	MCI due to AD	[redacted]	[redacted]
		Mild AD	[redacted]	[redacted]
		Moderate AD	[redacted]	[redacted]
		Severe AD	[redacted]	[redacted]
		Death	[redacted]	[redacted]
	Mild AD (placebo: N=146, lecanemab: N=156)	MCI due to AD	[redacted]	[redacted]
		Mild AD	[redacted]	[redacted]
		Moderate AD	[redacted]	[redacted]
		Severe AD	[redacted]	[redacted]
		Death	[redacted]	[redacted]
		MCI due to AD	[redacted]	[redacted]

Visit	Baseline State	State at Corresponding Visit	Placebo n (%)	Lecanemab 10mg/kg Biweekly n (%)
	MCI due to AD or Mild AD (placebo: N=781, lecanemab: N=768)	Mild AD	[redacted]	[redacted]
		Moderate AD	[redacted]	[redacted]
		Severe AD	[redacted]	[redacted]
		Death	[redacted]	[redacted]
Week 65	MCI due to AD (placebo: N=625, lecanemab: N=593)	MCI due to AD	[redacted]	[redacted]
		Mild AD	[redacted]	[redacted]
		Moderate AD	[redacted]	[redacted]
		Severe AD	[redacted]	[redacted]
		Death	[redacted]	[redacted]
	Mild AD (placebo: N=145, lecanemab: N=150)	MCI due to AD	[redacted]	[redacted]
		Mild AD	[redacted]	[redacted]
		Moderate AD	[redacted]	[redacted]
		Severe AD	[redacted]	[redacted]
		Death	[redacted]	[redacted]
	MCI due to AD or Mild AD (placebo: N=770, lecanemab: N=743)	MCI due to AD	[redacted]	[redacted]
		Mild AD	[redacted]	[redacted]
		Moderate AD	[redacted]	[redacted]
		Severe AD	[redacted]	[redacted]
		Death	[redacted]	[redacted]
Week 79	MCI due to AD (placebo: N=620, lecanemab: N=580)	MCI due to AD	[redacted]	[redacted]
		Mild AD	[redacted]	[redacted]
		Moderate AD	[redacted]	[redacted]
		Severe AD	[redacted]	[redacted]
		Death	[redacted]	[redacted]
	Mild AD (placebo: N=141, lecanemab: N=141)	MCI due to AD	[redacted]	[redacted]
		Mild AD	[redacted]	[redacted]
		Moderate AD	[redacted]	[redacted]
		Severe AD	[redacted]	[redacted]
		Death	[redacted]	[redacted]
	MCI due to AD or Mild AD (placebo: N=761, lecanemab: N=721)	MCI due to AD	[redacted]	[redacted]
		Mild AD	[redacted]	[redacted]
		Moderate AD	[redacted]	[redacted]
		Severe AD	[redacted]	[redacted]
		Death	[redacted]	[redacted]

Abbreviations: AD, Alzheimer's disease; CDR, Clinical Dementia Rating; lecanemab, lecanemab 10 mg/kg biweekly; MCI, mild cognitive impairment; placebo, placebo.

d) Please elaborate whether a mapping function between CDR-SB and MMSE is available.

Company response: The company is not aware of published mapping functions between CDR-SB and MMSE, however this is not based on a formal literature search. One study identified through an online search, which examined the relationship among raw scores, reported that CDR-SB and ADAS-Cog are more precise in measuring the severity of cognitive dysfunction than the MMSE.[31]

e)Please elaborate on the implications (including the potential impact on the cost-effectiveness results) of using CDR-SB defined health states (instead of MMSE).

Company response: In line with the limitations of MMSE described in response to part b) of this question relative to CDR-SB, this suggests that use of CDR-SB to define health states and AD progression in the economic model will provide a more accurate representation of disease progression in the early AD population, particularly MCI due to AD.

f) Please provide numbers of patients in the MMSE defined health states at baseline, end of follow-up and any other measurement points in Study 201 and comment on any differences between the distribution of patients observed there and in Clarity AD.

Company response: In line with the limitations of MMSE described in response to parts b) and e) of this question relative to CDR-SB, this information has not been provided.

g) Please implement a scenario analysis using the transition probabilities and hazard ratio as derived from Study 201.

Company response: In line with the limitations of MMSE described in response to parts b) and e) of this question relative to CDR-SB, this information has not been provided.

h) 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.

Company response: As described in the CS, key criteria to select studies from the SLR and other literature searches to parametrise the economic model included location and health state definitions, with UK studies defining health states based on CDR-SB being preferred. In some instances, such studies were not identified, potentially due to CDR-SB (which measures cognition and function) being adopted more recently than other AD severity scales such as MMSE (which only measures cognition). In situations where studies defining health states based on CDR-SB were not available, UK studies were preferred.

i) Please elaborate on the transferability of health state utility values and costs data categorised based on the MMSE to CDR-SB defined health states.

Company response: Clinical expert opinion was sought to inform the response to this question. In summary, feedback was that this is a complex topic, particularly given MMSE only measures cognition whereas CDR-SB measures cognition and function, and with carer input. One expert commented that it is reasonable to transfer between MMSE and CDR-SB, however there is strong preference for CDR-SB.

In light of this feedback and responses to other parts of this question, the company believes it is appropriate to transfer health state utility values and costs data categorised based on the MMSE to CDR-SB defined health states, however acknowledges this may induce some uncertainty in the economic model.

j) Please elaborate on the implications (including the potential impact on the cost-effectiveness results) of CDR-SB defined health states.

Company response: In line with the response to part e) of this question, use of CDR-SB should generate a more accurate representation of disease progression in the early AD population, particularly MCI due to AD, enhancing the relevance of the cost-effectiveness results. This also ensures the clinical outcomes estimated by the economic model can be validated directly against the primary endpoint of the Clarity AD study, as presented in the CS and in response to question B28, without the need for mapping.

k) Please provide scenario analyses, as well as an updated version of the economic model, using MMSE to define health states.

Company response: In line with the response to multiple parts of this question, this functionality has not been incorporated in the economic model.

B 6. In CS section B.3.2.3.2, it is stated that "Backwards transitions (i.e., to milder health states) are permitted, as observed in Clarity AD".

a) Please clarify that this in line with common modelling practices in AD.

Company response: Backwards transitions were permitted in the model, as observed in Clarity AD and published AD natural history data, and in alignment with clinical advice to the company from the July 2023 UK HTA advisory board that some patients may experience improvements in cognitive scores.[2,15,32] This is consistent with economic evaluations of DMTs in the published literature. Of the six cohort models discussed by Handels et al., three permitted backwards transitions to less severe health states Backwards transitions were also permitted in the evidence report on lecanemab published by ICER.[33]

b)Please justify this assumption of including backwards transitions given that according to expert opinion "such improvements are feasible but may only be temporary".

Company response: Inclusion of backward transitions was deemed appropriate in this context given the model uses a relatively short cycle length of one month, therefore such 'improvements' are likely to be temporary. As described in the CS, Document B, Section B.3.2.3.3, a key rationale for this cycle length was to reflect transient improvements to less severe health states which could not be accurately modelled using longer cycle lengths (e.g. one year).

Transitions to less severe health states are observed in many publications on the natural history of AD using a variety of databases, including the NACC, SveDem, and CERAD databases, despite being calculated using cycle lengths of one year.[34–36]

Due to the nature of a cohort model, it is not possible to track individual patients, however, the cohort progresses over time, on average. For example, the per-cycle probability of transitioning backwards from 'mild AD' to 'MCI due to AD' from the Potashman (NACC) data (0.3%) is low compared with the annual probability of

transitioning forward to ‘mild AD’ from ‘MCI due to AD’ (1.5%). This is true for the equivalent relationships in all health states.

c)Please clarify how these backwards transitions were included in the CS model and elaborate whether these improvements are indeed modelled to be temporary.

Company response: From 0-18 months in the CS model, backwards transitions are modelled as observed in Clarity AD (see Table 39 of the CS). Beyond 18 months, data from Potashman et al. were used to inform all transitions for standard of care (see Table 40 and Table 41 of the CS).[15] The treatment effect of lecanemab vs. standard of care (hazard ratio for time to worsening) is conservatively applied to forwards transitions only, therefore, the rate of backwards transitions is equivalent in both arms for the remainder of the time horizon

These improvements are only temporary because the probability of transitioning forward to a more severe health state is greater than the probability of transitioning backward to a less severe health state, in all health states, meaning the cohort progresses over time, on average. Please refer to response to part b) for further details.

Treatment effectiveness

B 7. The company use the baseline characteristics from the ITT population in the model. However, it seems as though the baseline characteristics that were shown to clinical experts for validation (and deemed appropriate) were from the mITT population.

a) The proportions of patients in mild AD versus MCI due to AD differed significantly between ITT and mITT populations. Please elaborate (with supporting evidence) on the generalisability of the baseline characteristics based on the ITT as well as mITT, to the UK population?

b) Can the company provide supplementary evidence on the proportions of mild AD versus MCI due to AD in patients eligible for treatment with lecanemab in UK clinical practice (i.e. Abeta population), either producing data if available, or expert opinion?

Company response (parts a) and b)): To respond to this question, UK clinical expert feedback was sought on the generalisability of the Clarity AD population to UK clinical practice, specifically regarding the proportions of patients with MCI due to AD (61.5%) vs mild AD (38.5%) in the Aβ positive population expected to be treated with lecanemab.

One clinician stated that whilst the proportions observed in Clarity AD are unreflective of the proportions of people who have MCI due to AD vs. mild AD in the UK population, there are broadly reflective of the proportions of people who are eligible for lecanemab over time. Another clinician stated that the proportions of mild AD versus MCI due to AD will change a lot over time with the spread of brain health clinics and access to blood-based biomarkers, so the proportions seen in Clarity AD are likely to reflect what will be seen in UK clinical practice. A third clinician stated the prevalence of MCI due to AD is not known, initially would expect the proportion to be lower in these patients until the mechanism to identify them and pathway is improved. They would expect the initial population to be weighted more towards mild AD as those patients are more reliably followed up. Over time the proportion of MCI due to AD patients is expected to increase.[10]

B 8. PRIORITY QUESTION The company derived transition probabilities in the first 18 months of the model time horizon from Clarity AD. We would like clarification about the analyses:

a) Please list all transition probabilities that are incorporated in the CS model, including the source, a brief description of how they were calculated, and a justification for that method for each.

Company response: Table 57 lists all transition probabilities used in the model and their data sources.

From 0-18 months in the model, data from Clarity AD were used to inform transitions from the MCI due to AD and mild AD health states. Clarity AD provided randomised, direct evidence for the comparison of interest, and was therefore considered the most robust source of evidence to inform transitions in the first 18 months of the model. Transition probabilities were calculated from the baseline and 18-month distributions of patients across each health state based on CDR-SB. The calculation

of the one-month transition probabilities from 18-month Clarity AD data is described in response to part b) of this question.

As the core study duration was 18 months, and only [redacted]% patients in the placebo arm progressed to moderate AD during the 18-month follow-up, a systematic literature review (SLR) was conducted to identify published data on the natural history of AD to supplement Clarity AD data for the economic analysis.

As detailed in B.3.3.1.2 of the CS, based on the SLR, none of the 40 studies identified were specific to the UK. Only three studies reported results for a population with confirmed Aβ pathology. Potashman et al. reports transition probabilities between clinically defined stages of AD across the entire spectrum of disease from MCI due to AD to severe AD, and defines disease stages by CDR-SB, aligning with the health state definitions used in this analysis (CS Section B.3.2.3.1).[15] Potashman et al. was therefore considered the only appropriate source of natural history data for use in this analysis, in absence of any UK-specific data.[15]

Calculation of transition probabilities from Potashman et al. was performed in the same way as for months 0-18. The annual transition probabilities reported in the publication were re-calculated by subtracting the probability of mortality (which was applied separately in the analysis based on adjusted general population life-tables) and removing the probability of transitioning to the asymptomatic health state (which occurred only from MCI due to AD) by adding these to the probability of remaining within the MCI due to AD health state, before converting to one-month transition probabilities.

Table 57: One-month transition probabilities used in economic model

Transition	SoC	Lecanemab	Source
0-18 months			
From MCI due to AD			Clarity AD[2]
to Mild AD	[redacted]	[redacted]	
to Moderate AD	[redacted]	[redacted]	
to Severe AD	[redacted]	[redacted]	
From Mild AD			
to MCI due to AD	[redacted]	[redacted]	
to Moderate AD	[redacted]	[redacted]	
to Severe AD	[redacted]	[redacted]	
Month 18+			
From MCI due to AD			Potashman et al., 2021[15] Hazard ratio for time to worsening for lecanemab vs placebo applied to forwards transitions to derive the lecanemab probabilities.
to Mild AD	1.5%	[redacted]	
to Moderate AD	0.5%	[redacted]	
to Severe AD	0.0%	[redacted]	
From Mild AD			
to MCI due to AD	0.3%	[redacted]	
to Moderate AD	3.5%	[redacted]	
to Severe AD	0.4%	[redacted]	
From Moderate AD			
to MCI due to AD	0.0%	[redacted]	
to Mild AD	0.2%	[redacted]	
to Severe AD	4.4%	[redacted]	
From Severe AD			
to MCI due to AD	0.0%	[redacted]	
to Mild AD	0.0%	[redacted]	
to Moderate AD	0.2%	[redacted]	

b) Please provide detail on how the transition probabilities were derived and calculated in both Clarity AD treatment arms, including the backward transition probabilities.

Company response: Transition probabilities based on Clarity AD were calculated by transforming the 18-month patient count data to monthly probabilities. For example, for transitions from MCI due to AD to mild AD:

- 18-month transition probability = number of patients in the mild AD state at 18 months who were MCI due to AD at baseline / total number of patients in the analysis
- Monthly transition rate = –ln(1–[18-month transition probability])/18
- Monthly transition probability = 1–exp (–monthly transition rate)
- The probability of remaining in the current health state was set equal to one minus the sum of the probabilities of leaving the health state.

c) Please justify (providing supporting evidence) that the assumption that transition probabilities are constant is reasonable, including visual presentation of time-to-event data, and health state occupation at baseline, 3, 6, 9, 12, 15, 18 months (both % and N).

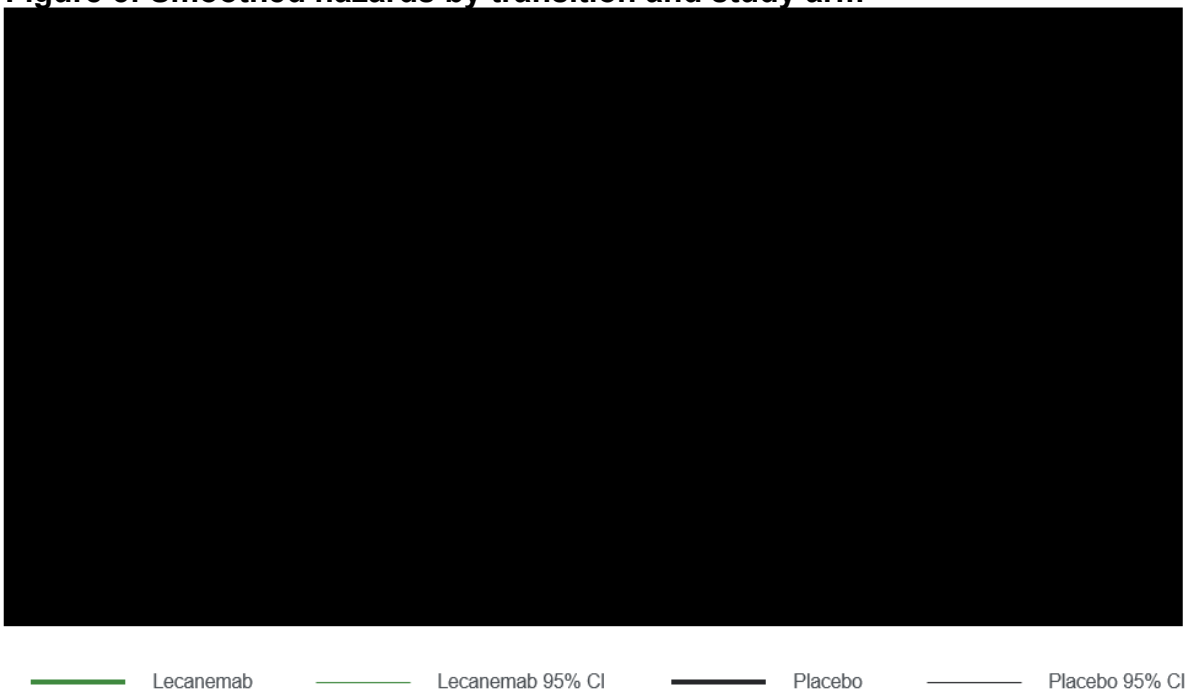
Company response: Health state occupation by visit is reported in Table 56. A summary of the cumulative event rate for each transition and study arm is presented in Figure 4 and the smoothed hazards for each transition and study arm are presented in Figure 5.

There is a trend towards an increase in the rate at which transitions from MCI due to AD to mild AD, mild AD to moderate AD, and mild AD to MCI due to AD (transitions 1-3 in Figure 5) occur over time during Clarity AD; for these transitions there appears to be a further increase in the event rate towards the end of the study, which may be an artefact of low numbers of patients at risk beyond year 1.5. Data for transition 4 is based on a limited number of observations (see Figure 4), and is therefore difficult to draw conclusions from.

Figure 4: Cumulative event rate by transition and treatment

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

Figure 5: Smoothed hazards by transition and study arm



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

d)Please perform survival analysis to inform transitions between health states based on the observed trial data, and fit parametric distributions to

health state occupancy over time data, according to NICE TSDs 14 and 21.

Company response: A multistate survival model was developed to estimate transition probabilities over time. Multistate models have been used in the context of Alzheimer's disease previously. For example, Robitaille et al estimate a four-state model which illustrates the effect of high versus low education on cognitive functioning.[37]

Health state membership was converted into time-to-event data, with 'events' being defined as movements (transitions) into new health states. The structure of the multistate survival model is presented in Figure 4. Transitions to severe AD and death were not included due to the low number of observed events in Clarity AD. Transitions to severe AD were informed by Potashman et al., and transitions to death were informed by Crowell et al as per the updated company base case.[15,38] Where a patient moved across two health states between observations (e.g. from MCI due to AD to moderate AD), the patient was assumed to have moved to the intermediate health state at the mid-point between the two observations. Time in the analysis was time from baseline in Clarity AD.

The analysis was conducted using a clock-forward (Markov) approach to enable time-dependent transition probabilities to be incorporated in the existing model structure without tunnel states, which would not have been feasible within the time timeframe for clarification question responses.[39]

Figure 6: Multi-state survival model structure

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

Figure 7 presents the log-cumulative hazard by transition and study arm. Treatment arm curves are generally parallel for each transition, therefore a joint (i.e. dependent) modelling approach was used, in which the treatment effect was represented by a covariate within the survival model for each transition and was assumed to be

constant on the associated scale. This was further supported by the smoothed hazard plots presented in response to part c), and the proportional hazards assessment for the time-to-worsening analysis detailed in response to question B11a, which indicated the assumption was valid.

Figure 7: Log-cumulative hazards, by transition and treatment

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

Separate statistical models were estimated for each transition. Six distributions were considered (exponential, Weibull, generalised gamma, Gompertz, log-normal, and log-logistic). Plots of observed vs predicted transition probability are presented in Figure 8 - Figure 11. Given a clock-forward approach was used, observations are considered using time from the start of the study (i.e. at baseline) for each patient, as opposed to time since entry into each health state. Consequently, the numbers at risk are increasing for all transitions other than transition 1, and increasing from zero for transition 4 (Figure 11) given no patients started Clarity AD with moderate AD.

Based on visual inspection of the observed vs predicted transition probabilities, the exponential model provided the poorest fit for transitions 2 (mild AD to moderate AD), and to a lesser extent transitions 1 and 3. The Akaike (AIC) and Bayesian Information Criterions (BIC) diagnostic scores are presented in Table 58 for each transition, and when using the same distribution for all transitions. These also suggest the exponential model provides a relatively poorer fit compared to other models for transitions 1-3.

Figure 8: observed vs predicted transition probability (transition 1)

Figure 9: observed vs predicted transition probability (transition 2)

Figure 10: observed vs predicted transition probability (transition 3)

Figure 11: observed vs predicted transition probability (transition 4)

Table 58: AIC and BIC statistics for each transition

Distribution	All transitions	Transition 1 (MCI to mild AD)	Transition 2 (Mild AD to moderate AD)	Transition 3 (Mild AD to MCI)	Transition 4 (Moderate AD to mild AD)
Akaike Information Criterion					
Exponential	5061.1	2876.4	747.4	1345.8	**91.6**
Generalised gamma	4853.8	2740.9	712.2	1306.5	94.1
Weibull	4892.5	2767.2	**711.1**	1320.9	93.3
Gompertz	4936.8	2800.2	711.7	1331.9	93.0
Log-logistic	4891.6	2767.3	712.2	1318.1	94.0
Log-normal	**4854.6**	**2739.3**	716.6	**1305.2**	93.5
Bayesian Information Criterion					
Exponential	5097.5	2887.3	757.4	1355.8	**97.0**
Generalised gamma	4926.6	2762.8	732.3	1326.6	105.0
Weibull	4947.1	2783.6	**726.1**	1336.0	101.4
Gompertz	4991.4	2816.6	726.8	1346.9	101.1
Log-logistic	4946.2	2783.7	727.3	1333.1	102.1
Log-normal	**4909.2**	**2755.7**	731.7	**1320.2**	101.6

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

Overall, the exponential distribution was identified as the optimal distribution for transition 4 in the model based on the AIC/BIC statistics and given the small number of patients at risk for this transition.

For the remaining transitions (1-3), the generalised gamma distribution (Figure 12), the log-normal distribution (Figure 13), and the log-logistic distribution (Figure 15) estimate decreasing probabilities of transition from MCI to mild AD and from mild AD to MCI after approximately 6 months, which is inconsistent with the smoothed hazard plots (Figure 5), hence these distributions were deemed inappropriate. The Gompertz distribution was also dismissed as the long-term transition probabilities beyond two years appeared implausible since the risk of transitioning from mild AD to moderate AD and from mild AD to MCI sum to more than 1 from approximately four years onwards (Figure 14). In contrast, the Weibull distribution estimates increasing probabilities of transitions 1-3 (Figure 17), consistent with the hazard plots in Figure 5, which appeared plausible in the short- and long-term. The Weibull

distribution was therefore deemed most appropriate for modelling transitions 1-3, despite not providing the best fit based on AIC/BIC.

Results of a scenario analysis exploring the use of the Weibull distribution for transtions 1-3 and the exponential distribution for transition 4 are provided in response to part e) of this question.

Figure 12: Generalised gamma (transition 1-3), exponential (transition 4) – 18 months

Abbreviations: Lec – lecanemab; MCI – mild cognitive impairment.

Figure 13: Log-normal (transition 1-3), exponential (transition 4) – 18 months

Abbreviations: Lec – lecanemab; MCI – mild cognitive impairment.

Figure 14: Gompertz (transition 1-3), exponential (transition 4) – lifetime horizon

Abbreviations: Lec – lecanemab; MCI – mild cognitive impairment.

Figure 15: Log-logistic (transition 1-3), exponential (transition 4) – 18 months

Abbreviations: Lec – lecanemab; MCI – mild cognitive impairment.

Figure 16: Exponential distribution for all transitions – 18 months

Abbreviations: Lec – lecanemab; MCI – mild cognitive impairment.

Figure 17: Weibull (transition 1-3), exponential (transition 4) – 18 months

Abbreviations: Lec – lecanemab; MCI – mild cognitive impairment.

Figure 18: Weibull (transition 1-3), exponential (transition 4) – lifetime horizon

Abbreviations: Lec – lecanemab; MCI – mild cognitive impairment.

e) Please elaborate on the potential impact of relaxing the assumption of constant transition probabilities, ideally providing a scenario analysis in which transition probabilities over time follow a pattern as observed in Clarity AD, potentially using tunnel states.

Company response: Based on the analysis presented in part d), a scenario is presented in which transition probabilities during months 0-18 are predicted by the multistate survival model described previously. Based on the response to part d), the exponential distribution was used for the transition from moderate AD to mild AD, and the Weibull distribution was selected for transitions from MCI to mild AD, mild AD to moderate AD, and mild AD to MCI. The resulting transition probabilities during month 0-18 are presented in Table 59, and results of the scenario analysis are presented in Table 54. This scenario results in a decrease of £[redacted] ([redacted] compared with the corrected base case list price ICER, to £[redacted]. The associated PAS ICER is £[redacted].

The extrapolated curves and the associated long-term transition probabilities should be treated with caution, as these are based only on 18 months of data and therefore any over-fitting may lead to transition probabilities beyond 18 months which are not

representative of the underlying risk. In contrast, the NACC database has 12 years of follow-up and is therefore likely a better source for long-term natural history.[40]

Table 59: Multistate model transitions probabilities, 18 months

Cycle (months)	Lecanemab				SoC			
	MCI to Mild AD	Mild AD to MCI	Mild AD to moderate AD	Moderate AD to mild AD	MCI to Mild AD	Mild AD to MCI	Mild AD to moderate AD	Moderate AD to mild AD
1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
7	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
8	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
9	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
10	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
11	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
13	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
14	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
15	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
16	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
17	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
18	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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

f) The company did not use the ITT population for the estimation of transition probabilities and stated that "patients who did not complete the core study due to early discontinuation from adverse events, withdrawal of consent, or loss to follow-up did not attend the study visit at month 18, and therefore did not have data imputed and were excluded from the analysis." Please clarify what population was used, i.e. e.g. the safety population, and show how the patient baseline characteristics and health state occupancy of these patients compared to that of the ITT FAS+ population.

Company response: The population from which transition probabilities were derived was the ITT FAS+, excluding those described in the question. As discussed in the Updated company base case section at the beginning of Section B, the updated economic model uses the 81-week patient count data for health states using CDR-SB as presented in Table 50, rather than the 79-week data that was used in the original CS. These data more accurately reflect the ITT FAS+ sample sizes (lecanemab, N=849; placebo, N=868 at week 81, vs. lecanemab, N=[redacted]; placebo, N=[redacted] at week 79), as some patients attended their final visit more than one week later than was outlined in the protocol.

As only [redacted] patients in the lecanemab arm and [redacted] patients in the placebo arm were not included in this population, baseline characteristics are assumed to remain largely unchanged compared with the ITT FAS+ population, so this has not been provided separately.

g)Omitting these patients may bias the transition probabilities, likely in favour of lecanemab, as more patients discontinued in the lecanemab arm as compared to the placebo arm. Please explore in a scenario analysis the inclusion of discontinued patients by a type of worst-case imputation (e.g. assuming these had progressed to moderate AD) to explore the potential impact of excluding these observations.

Company response: This scenario results in an increase of £[redacted] ([redacted] compared with the corrected base case list price ICER, to £[redacted] (Table 54). The associated PAS ICER is £[redacted]

h) Please provide results of a scenario where only trial data are used and extrapolated over the model time horizon.

Company response: Direct patient counts over 18-months from Clarity AD were used to inform transition probabilities for the duration of the lifetime horizon for this scenario. This scenario results in a decrease of £[redacted] compared with the corrected base-case list price ICER, to £[redacted] (Table 54). The associated PAS ICER is in this scenario is £[redacted], a [redacted] decrease.

Additionally, an exploratory scenario was implemented in which the exponential distribution was used for the transition from moderate AD to mild AD and the Weibull distribution was used for the other transitions estimated by the multistate survival model, following the conclusions in response to part d) of this question. This scenario results in an increase of £[redacted] compared with the corrected base-case list price ICER, to £[redacted] (Table 54). The associated PAS ICER is in this scenario is £[redacted], a [redacted] increase.

B 9. PRIORITY QUESTION The natural history of AD was informed using NACC data as reported in Potashman et al to inform transition probabilities beyond 18 months in the economic model.

a) Please comment on alternative datasets and approaches being used for the modelling of AD natural history in the models that were compared in the Handels et al. 2022 (https://doi.org/10.1002/alz.12811) article, also referenced by the company.

Company response: The datasets used for AD natural history in the various models compared in Handels et al. are provided in Table 60. The most commonly used data source was NACC, which aligns with the CS base case. Other features of the modelling approaches are compared in response to Question B30.

As detailed in the CS, Document B, Section B.3.3.1, the key criterion for selection of a source of natural history data was a population consisting only of those with confirmed Aβ pathology. The FEM model used the US Health and Retirement study to provide longitudinal data but this did not include solely Aβ positive patients and progression in this model was reflected by mortality, rather than progression to more severe health states as defined by CDR-SB.[41] Herring et al., the LipDiDiet trial, and

the GERAS study also did not consider an Aβ positive population.[42,27,43] Vos et al. and the Rotterdam Study used by MICAN were not deemed appropriate datasets for the modelling of AD natural history in the model since they used MMSE to define health states rather than CDR-SB.[44] The AD-ACE model utilised the ADNI dataset, the generalisability of which is uncertain due to selection bias such as the exclusion of many comorbid conditions, as discussed in the CS, Document B, Section B.3.3.1.

Table 60: Alternative datasets used from Handels et al.

Model	AD natural history data source
IPECAD[45]	NACC data
SveDem[35]	Vos et al. and Swedish dementia registry
KP[46]	Vos et al. And Kungsholmen project
FEM[41]	Health and retirement study
Herring[42]	The French Paquid cohort, donepezil trials
ADACE[47]	ADNI
BASQDEM[27]	LipiDiDiet trial
MISCAN[48]	Rotterdam Study dementia, pooled memory clinic data
Davis[34]	NACC data
CPEC[49]	Vos study, NACC data
Jutkowitz[50]	NACC data
CEM[43]	GERAS data

Abbreviations: ADACE – Alzheimer's Disease Archimedes condition event simulator; BASQDEM – Basque Discrete-event simulation; CEM – Cost-effectiveness model; CPEC – Care Policy Evaluation Centre; FEM – Future Elderly Model; IPECAD – International Pharmacoeconomics Collaboration Alzheimer's Disease; KP – Kungsholmen Project; MISCAN – Microsimulation Screening AnalysiS; NACC – National Alzheimer's Coordinating Center; SveDem – Swedish Dementia Registry.

b) Please comment on the generalisability of the population (considered by Potashman et al) and the treatment they received to the UK clinical setting, also supporting this with evidence and/or expert opinion?

Company response: To help answer this question, UK clinical expert feedback was sought on the generalisability of the population considered by Potashman et al. to the UK early AD population.

In summary, use of symptomatic AD treatment observed in Potashman et al. was deemed generally consistent with UK clinical practice by all three experts, supported by data from the 2019 UK national memory clinic audit, although one cited use in MCI due to AD may be lower in UK practice (see response to question B4). Additional similarities to UK memory clinics cited by one expert were proportions of *APOE4* carriers and rates diabetes and cardiovascular disease.[51]

Differences identified were that the UK population would be expected to be younger, have more comorbidities and have lower educational attainment than Potashman et al. Severity of disease was also cited however this is not expected to impact the generalisability of Potashman et al. given these inform AD health state transition probabilities.

Overall, based on this feedback from the clinical experts, the company believes the population in Potashman et al. is generalisable to UK clinical practice.

c) Please comment on the appropriateness of assuming constant transition probabilities beyond the 18 months observed trial data and provide supporting evidence, i.e. visual presentation of time-to-event data or health state occupation at different timepoints (both % and N) from the NACC database. Please consider fitting parametric distributions according to NICE TSDs 14 and 19. Please also provide expert opinion on the rates of disease progression over time.

Company response: As discussed in the CS, Document B, Section B.3.3.1.2, Potashman et al. was the only suitable source of natural history data aligning with the decision problem, however this only reports constant transition probabilities. Neither time-to-event data nor health state occupation are available from Potashman et al., and the company do not have access to the NACC database. It was therefore not possible to fit parametric distributions to the natural history data.[15]

A comparison of mean time in each health state based on the multistate model described in response to B8 part d) and switching to Potashman et al data at 1.5, 5, and 30 years has been compared with using natural history data from Potashman et al. for the full time horizon (Table 61).[15] Time spent in moderate AD and severe AD is very similar between the two approaches, and although differences are observed for MCI due to AD and mild AD, total life-years are similar. As described in response to B8 part h), the multistate analysis life-year estimates may be limited by the extrapolation of 18-month data from Clarity AD over lifetime (30 years) and the associated uncertainty in the long-term transition probabilities. Therefore, the company maintain that modelling constant transition probabilities beyond 18 months based on Potashman et al. is appropriate given the follow-up provided by this study.

The company was not able to elicit expert opinion on the rates of disease progression over time within the timeframe of these responses.

Table 61: Comparison of mean time in health state, natural history vs. multistate model

Health state	Total life years				
	Natural history data only	Base case (Clarity data up to 1.5 years)	Multistate (switch at 1.5 years)	Multistate (switch at 5 years)	Multistate (switch at 30 years)
MCI due to AD	3.15	[redacted]	[redacted]	[redacted]	[redacted]
Mild AD	1.42	[redacted]	[redacted]	[redacted]	[redacted]
Moderate AD	1.25	[redacted]	[redacted]	[redacted]	[redacted]
Severe AD	2.06	[redacted]	[redacted]	[redacted]	[redacted]
Total	**7.88**	[redacted]	[redacted]	[redacted]	[redacted]
Difference vs. using natural history data only					
MCI due to AD		[redacted]	[redacted]	[redacted]	[redacted]
Mild AD		[redacted]	[redacted]	[redacted]	[redacted]
Moderate AD		[redacted]	[redacted]	[redacted]	[redacted]
Severe AD		[redacted]	[redacted]	[redacted]	[redacted]
Total		[redacted]	[redacted]	[redacted]	[redacted]

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

d) Please implement a scenario using an alternative approach, for example by implementing an alternative way of modelling progression that takes account of time-varying transition probabilities, potentially using tunnel states.

Company response: As detailed in the response to part c) of this question, Potashman et al. was the only suitable source of natural history data aligning with the decision problem, however this paper does not report data to inform time-varying transition probabilities, therefore the company are unable to incorporate this using data from Potashman et al.

The only time-varying transition data available to the company was time-varying analysis conducted in response to B8 d) and h), in which survival analysis was performed on Clarity AD data. Please refer to B8h) for the results of this scenario.

e) Please explain why the transitions to death were not sourced based on Potashman et al.

Company response: Potashman et al. report annual transition probabilities to death from each health state among an incident population, however this is expressed as a single probability of death based on current health state, hence does not vary over

time nor account for sex.[15] As the rate of mortality would be expected to increase with age independently of disease progression, this approach was not considered to be suitable for extrapolation over a lifetime.

f) Please explore using the transitions to death based on Potashman et al in a scenario.

Company response: A scenario has been included that used the transitions to death based on Potashman et al.[15] In this scenario, the risk of death is constant. As described in response to part e) of this response, a constant risk of death in any given health state was not considered appropriate given mortality is known to be age-dependent. Results of the scenario analysis are presented in Table 54. This scenario results in an increase of £[redacted] compared with the corrected base-case list price ICER, to £[redacted]. The associated PAS ICER is in this scenario is £[redacted], a [redacted] increase.

B 10. PRIORITY QUESTION There appear to be technical errors in the estimation of transition probabilities to multiple health states and their conversion to a different period length matching the cycle length. This can introduce significant errors in the calculation of numbers of patients in each health state as illustrated by Gidwani et al, in particular Section 5.2 (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7426391/). Please follow the tutorial described in the Gidwani et al article and implement the correction in a revised model file.

Company response: The wording of the question implies an error had been identified in the CS model, however it was acknowledged by the EAG during the clarification TC on 10th January 2024 that no specific errors had been identified. The rationale for the question was for the company to follow the approach described by Gidwani et al to check if there were errors in the estimation of transition probabilities.[52]

In the CS model, the transition probabilities were transformed to monthly cycles from the annual probabilities reported by Potashman et al. as described in the response to Question B8, consistent with the approach described by Gidwani et al.[52] Gidwani et al. describe that this method of estimating the conversion may introduce errors when more than two transitions can occur within a cycle, suggesting three solutions:

1) Revise the model structure so that each node only has two model transitions.

2) Calculate the eigen decomposition of the transition matrix.

3) Where there are only three possible transitions, and two of the probabilities are small, and the cycle length is shorter than the published cycle length, the error may be small.

Based on the above solutions, only option 2 was considered relevant to the current model structure. Option 1 would not be possible, as this would require severely limiting structural assumptions, for example restricting patients movement so that patients can only remain in their current health state, or progress to the next most severe health state in any given cycle, which would not be consistent with the natural history data (for example, Potashman et al. includes probabilities of increasing in disease severity such that a health state is skipped, e.g., progressing from MCI due to AD straight to moderate AD.[15] Similarly, option 3 is only feasible with three possible transitions.

The eigen decomposition of the transition matrix was estimated, however this resulted in negative transition probabilities for some transitions, as forewarned by Gidwani et al. We considered that the resulting transition probabilities therefore lacked face validity, thus a scenario was performed in which these negative transition probabilities were assumed to be 0. Results based on this analysis are presented in Table 54. This scenario results in a decrease of £[redacted] compared with the corrected base-case list price ICER, to £[redacted]. The associated PAS ICER is in this scenario is £[redacted], a [redacted] decrease.

It is correct that the approach used in the base-case does not explicitly account for competing risks, but the resulting transition probabilities appear to have greater face validity than those estimated using the eigen decomposition approach, whilst providing similar model predictions and results.

B 11. PRIORITY QUESTION The treatment effect of lecanemab versus SoC applied after 18 months was based on Clarity AD and applied to the transition probabilities from Potashman et al using a hazard ratio. This hazard ratio was derived using a Cox proportional hazard model for transitions from MCI due to

AD to mild AD and from mild AD to moderate AD. The company also assumed no treatment waning while patients are modelled to be on treatment and [redacted] waning upon treatment discontinuation in the model. This assumption was made as there is no evidence from Clarity AD regarding the long treatment effects beyond the 18th month.

a) Please comment on the appropriateness of a Cox-proportional hazards model for the estimation of the hazard ratios in the transitions from MCI due to AD to mild dementia and from mild dementia to moderate dementia, and provide supporting data for this in line with TSD 14 and 21.

Company response: The log-cumulative hazard plot and Schoenfeld residuals for time to worsening of disease progression are presented in Figure 19 and Figure 20 for the MCI due to AD and mild AD populations, respectively. The log-cumulative hazards are parallel following the start of the study, and testing of the Schoenfeld residuals show no evidence that the proportional hazards assumption is violated (p=[redacted] and p=[redacted] for the MCI due to AD and mild AD populations, respectively).

Based on these findings, the proportional hazards assumption holds and use of the semi-parametric Cox model to estimate the hazard ratios for the stated transitions is appropriate.

Figure 19: Log-cumulative hazards and Schoenfeld residuals (MCI due to AD)

[redacted]

Figure 20: Log-cumulative hazards and Schoenfeld residuals (Mild AD)

b) Please explain how time-to-worsening was defined, and also show whether it included patients that skipped a stage, e.g. progressed from MCI due to AD to moderate AD. Please elaborate on the implications on using time-to-worsening as the basis for estimating the treatment effect of lecanemab versus SoC.

Company response: Time-to-worsening was defined as CDR-SB score worsening from MCI due to AD at baseline to a worse health state (mild, moderate, or severe AD), or mild AD at baseline to a worse health state (moderate or severe AD). Health states were defined as per the economic model using CDR-SB; MCI due to AD 0.5 – 4.0, mild AD 4.5 – 9.0, moderate AD 9.5 – 15.5, and severe AD 16.0 – 18.0. Patients were considered to have had a worsening event at the time of the first CDR-SB observation where the associated criteria were met.

By applying the same time-to-worsening hazard ratio to all worsening health state transitions from a given health state, it is assumed that the treatment effect of lecanemab vs. standard of care is the same for all worsening health state transitions e.g. mild to moderate AD and mild to severe AD.

By using time-to-worsening to represent the treatment effects for lecanemab beyond 18-months, the analysis assumes that lecanemab has no effect on transitions to better health states (‘backwards transitions’). A higher rate of such transitions was

observed for lecanemab compared to placebo in Clarity AD, hence this approach may underestimate total QALYs for lecanemab and thus also underestimate incremental QALYs.

c)Please estimate hazard ratios at time points of months 3, 6, 9, 12, 15, 18 to explore the appropriateness of constant hazard ratios over time. Please plot the scaled Schoenfeld residuals over time, and add a trend line.

Company response: Table 62 presents hazard ratio by visit. The hazard ratio is calculated based on a Cox proportional hazards model using time to event data by target month. Patients were censored at visit +0.25 month in each model. The hazard ratio at 18 months shows the result using all time to event data in the Clarity AD Core study.

The hazard ratios become consistent with the month 18 analysis from approximately month 9. Scaled Schoenfeld residuals are presented in response to part a of this question.

Table 62: Hazard ratios for time-to-worsening by visit and population (defined by CDR-SB)

Visit	MCI due to AD	Mild AD
3 month	[redacted]	[redacted]
6 month	[redacted]	[redacted]
9 month	[redacted]	[redacted]
12 month	[redacted]	[redacted]
15 month	[redacted]	[redacted]
18 month	[redacted]	[redacted]

Abbreviations: AD – Alzheimer's disease; CDR-SB – Clinical Dementia Rating-Sum of Boxes; MCI – mild cognitive impairment

d) Please discuss the potential of treatment effect waning after 18 months and explore different treatment effect waning assumptions in scenario analysis.

Company response: Although the duration of the Clarity AD core study which informed the lecanemab treatment effect in the economic model was 18 months, 729 (81.2%) of lecanemab patients completed the study. Moreover, 671 patients randomised to lecanemab in the core study continued treatment with lecanemab in the OLE study.

Consistent with this, it is expected that patients will remain on treatment with lecanemab beyond 18 months in clinical practice, and the CS base case assumed continuation of treatment, yielding a mean time-on-treatment of 3.15 years. Consequently, and given the CS base case already assumes [redacted] treatment effect waning upon discontinuation due to disease severity, the company believes it would be inappropriate to also apply treatment effect waning after 18 months, hence this scenario analysis has not been conducted.

B 12. The company included a treatment stopping rule when patients progress to moderate AD and when they were institutionalised. The assumption of stopping treatment upon progression to moderate AD was due to the absence of data from Clarity AD, and similar to the Institute for Clinical Economic Review (ICER) assessment of lecanemab. The assumption of stopping the treatment upon institutionalisation was based on the clinical experts advisory board and was implemented in the base case regardless of the disease severity.

a) Please provide further justification and evidence for assuming the stopping of treatment when patients have been institutionalised regardless of their disease severity.

Company response: To help respond to this question, UK clinical expert opinion was sought. One expert stated that the number of exceptions to stopping treatment upon institutionalisation would be “extremely small”, and another cited post-op recovery as a potential exception. The second expert also stated it is very rare for patients with mild AD to enter institutional care.[10] The third expert did not respond to the question directly, but stated where the patient lives is less important than AD severity.

To further investigate this, the opinion of Alzheimer’s Research UK (ARUK), a leading AD charity in the UK, was sought to comment on the likelihood of patients stopping treatment once they have been institutionalised. ARUK stated that it is reasonable to assume that patients approaching the need for care facility admission would no longer meet the eligibility criteria for lecanemab, meaning treatment will have stopped well before advanced care needs arise.[53]

b) Please provide scenario analyses where treatment stopping rules are based on fixed treatment durations of 1.5, 3, and 5 years in line with Tahami Monfared et al. 2022. (https://link.springer.com/article/10.1007/s40120-023-00473-w)

Company response: As stated in Tahami Monfared et al., clinical trials of lecanemab show benefits of continuous treatment with lecanemab. As discussed in the CS, Document B, Section B.3.3.3, there is no consensus among UK clinical experts regarding exactly which stopping rule(s) will be applied in clinical practice. [redacted][54] The same sentiment can be applied to any time-based stopping rule.[55] As such, the company believe any fixed treatment duration scenario would be unreflective of anticipated UK clinical practice at this stage. Therefore, these scenarios have not been presented. [redacted]

B 13. Data for the rate of institutionalisation in the cost effectiveness model were informed by Knapp et al. 2016 in the base case and Belger et al. 2019 in a scenario analysis. Both studies reported risk of institutionalisation by AD severity according to MMSE and they were identified by hand search as these data were not available from Clarity AD and data identified through the natural history SLR were sparse. Individuals in the MCI due to AD health state were assumed to have zero risk of institutionalisation.

a) Please provide further details on the search strategy/keywords used in the hand search.

Company response: The hand search utilised simple search terms, including “Alzheimer’s”, “dementia”, “severity”, and “institutionalisation” in combination, and “Alzheimer’s”, “dementia”, “severity”, and “care home” in combination. The search engine utilised was Google Scholar. Papers were screened by title for relevance by a single reviewer. Those deemed relevant based on titles were reviewed in full by the

same single reviewer. Studies that did not include UK data were excluded. Those that reported UK data were reviewed for data on risk of institutionalisation by Alzheimer's disease severity.

b) Please elaborate on how the population for Knapp et al 2016 and Belger 2019 are reflective of the population of interest, also considering that the patient population was not amyloid positive.

Company response: As discussed in Document B, Section B.3.3.4, Knapp et al. 2016 is a UK-based study, and Belger et al. 2019 reports data for three European countries, including the UK. Knapp et al. 2016, which was used in the base case, analysed observational data for mental health clinical records for participants with AD (n=3,075) with data linkage to UK Hospital Episode Statistics (HES). Belger et al. 2019 is a prospective, non-interventional cohort study in 1,495 patients with AD. As this study includes patients outside of the UK, it was deemed less suitable than Knapp et al., hence was used only in scenario analyses. UK-based studies were deemed more appropriate than non-UK based studies, regardless of confirmation of amyloid beta (Aβ) pathology.

The Company acknowledge that the optimal source of rates of institutionalisation would be in a UK population with confirmed Aβ pathology, however no studies were identified for this specific population, nor in an Aβ positive population outside of the UK-setting. Consequently, Knapp et al. and Belger et al. were deemed the most appropriate studies for the reasons stated in the CS (Document B, Section B.3.3.4).

c) Gunnarsson et al 2016 (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4893835/) is a study which observed that extremely high levels of CSF total tau (t-tau) are associated with a higher risk of institutionalisation in patients with MCI due to AD and progression to moderate AD. These associations were dose-dependent and present already at the stage of MCI due to AD. Please provide further consideration of the rates of institutionalisation in this context and provide a scenario analysis that assumes admission to institution in the MCI due to AD stage is possible.

Company response: Gunnarsson et al. state that individuals in the highest quartile of CSF t-tau (≥900 ng/L) experienced the highest risk of institutionalisation, which

was also seen when including patients with MCI due to AD only, thus concluding that high CSF t-tau levels predict early nursing home placement.

In Clarity AD, mean CSF t-tau in patients with MCI due to AD at baseline was substantially lower than the highest quartile stated by Gunnarsson (mean [SD]: [redacted] ng/L [redacted] and [redacted] ng/L [redacted] for the lecanemab and placebo arms, respectively). Gunnarsson et al. report ORs for nursing home placement of 1.42 and 1.50 (for the crude analysis and multivariate analysis, respectively) for those with CSF t-tau between 511-680 (ng/L). However, this is not specific to patients with MCI due to AD and includes patients of any AD severity. The authors do not report an OR for patients with MCI due to AD only with CSF t-tau levels aligning with those observed in Clarity AD. As such, the company does not consider the risk of institutionalisation reported by Gunnarsson et al. for the MCI due to AD health state to be reflective of the Clarity AD population.

As the consensus reached by UK clinical experts at the July 2023 HTA advisory board was that patients with MCI due to AD would not be institutionalised and no contrary published evidence has been identified in a relevant population (including Gunnarsson et al.), this scenario analysis has not been conducted.

B 14. Mortality in the cost effectiveness model was based on hazard ratios vs. cognitively normal individuals as reported in Crowell et al. 201 which was identified by hand search and reported hazard ratios from the Uniform Data Set of the NACC database.

a) Please provide further details on the search strategy/keywords used in the hand search.

Company response: The hand search utilised simple search terms, including “Alzheimer’s”, “dementia”, “severity”, and “mortality” in combination. The search engine utilised was Google Scholar. Papers were screened by title for relevance by a single reviewer. Those deemed relevant based on titles were reviewed in full by the same single reviewer against the criteria specified in Document B, Section B.3.3.5; namely, mortality estimates for all model health states (MCI due to AD, mild, moderate, and severe AD, defined using CDR-SB), effects estimated relative to general population mortality rather than those on the absolute scale, and studies

reporting data for a population with confirmed Aβ pathology, for consistency with the source of transition probabilities for AD progression and the decision problem for this appraisal.

b) The model in Crowell et al. estimated a decreased risk of death in the MCI due to AD subgroup when compared with the cognitively normal group. Please further explain the plausibility of this assumption.

Company response: Crowell et al. acknowledge that relative mortality for the MCI due to AD health state compared with cognitively normal (CN) participants may have been underestimated. This is due to more restrictive eligibility criteria being required for the AD cohort than for the CN cohort; participants with a record of non-AD etiologic diagnosis potentially causing cognitive impairment before or at index were excluded from the AD cohort. However, Crowell et al. found no increase in mortality associated with MCI due to AD after controlling for confounding factors and disease progression over time. To account for the potential underestimation of risk of mortality from the MCI due to AD health state, the results of the scenario presented in the CS, in which a HR of 1 is used for this health state, are presented in Table 54. This scenario results in an increase of £[redacted] ([redacted]%) compared with the corrected base-case list price ICER, to £[redacted]. The associated PAS ICER is in this scenario is £[redacted], a [redacted]% increase.

c) Please provide a scenario analysis using the mortality rates from Monfared et al. 2022 study (https://link.springer.com/article/10.1007/s40120-023-00473-w)

Company response: Tahami Monfared et al. 2022 utilise disease severity-specific hazard ratios (HRs) applied to age-specific all-cause mortality. The HRs applied are sourced from Andersen et al. 2010, a population-based cohort study of participants aged between 65 and 84 years at baseline and living in Odense, Denmark.[56] Based on 14-year follow-up data (1992 to 2006), the study reported HRs adjusted for gender and age for patients with questionable/very mild dementia, mild dementia, moderate dementia and severe dementia, not specific to Alzheimer's disease nor in a confirmed Aβ positive population.

As the population in the Crowell et al. reflects the Aβ positive population of interest, and reports risk of mortality according to health states defined by CDR-SB, the

company do not believe the proposed scenario analysis would be appropriate and have therefore not provided this scenario.

Adverse events

B 15. No adverse event (AE) disutilities were included in the economic analysis due to the impact assumed to be captured in HRQoL measures.

a) Please discuss the plausibility of excluding AE disutilities, given that HRQoL was only measured in intervals of 6 months and the expected major impact of ARIA-E and ARIA-H on HRQoL.

Company response: The utility analysis using Clarity AD data presented in the economic model calculates utility values by treatment arm. As such, this implicitly captures the impact of AEs on HRQoL for patients in each treatment arm, which is then reflected in the health state utility values (HSUV). The company acknowledge that the frequency of data collection may mean the full impact of AEs is not captured, however, applying disutilities in addition to treatment-specific HSUVs is likely to result in double-counting of the impact of AE disutilities.

b) Please provide updated economic model and scenario analysis including AE disutilties.

Company response: A scenario analysis including AE disutilities is presented in Table 54. The inputs for this scenario are presented in Table 63. This scenario results in a [redacted]) compared with the corrected base-case list price ICER, to [redacted]. The associated PAS ICER is in this scenario is [redacted]

Sourcing disutility values for ARIA-E and ARIA-H is challenging, as ARIA is a unique to amyloid-modifying therapies hence is not an established adverse event in clinical practice. As such, proxy adverse event disutilities have been used. Disutility values for ARIA-H and ARIA-E were sourced from Meckley et al., (2010) and Sullivan et al., (2006), respectively.[57,58] The ARIA-H utility decrement is a transient ischemic attack proxy value taken from Meckley et al., a published model assessing anticoagulation care. Sullivan et al. pooled data from 38,678 US patients across multiple disease areas to estimate the incremental disutility of chronic conditions in the US; they

report a mean utility decrement for transient cerebral ischemia, which was used as a proxy for ARIA-E. Disutility values for infusion related reactions were sourced from Boye et al., (2011).[59] This study considered Scottish patients with type 2 diabetes who participated in standard gamble interviews to evaluate the utility, or disutility, of three injection-related attributes including dose frequency, dose flexibility, and injection site reactions.

These disutilities were combined with durations of each event to generate a QALY decrement. Durations for each disutility were not available in the published literature, therefore these were informed by clinical expert opinion (as detailed in response to Question B27b). The duration of an ARIA event was based on one clinicians feedback that a patient with severe ARIA would be hospitalised for 5-7 days. The duration of IRR was based on the same clinicians feedback that symptoms or IR would last for 2-4 hours. The median was taken for each.[60]

It was assumed that mild and moderate AEs did not significantly impact patient HRQoL and therefore were assumed to incur no disutility. This is in line with previous NICE appraisals, such as TA784, TA931, and TA833, where only grade ≥3 treatment-related AEs were assumed to have an impact on the HRQoL of patients.[61–63] While a proportion of ARIA incidence in Clarity AD was asymptomatic, due to the negligible impact of disutilities on the ICER, incidence of ARIA was conservatively not corrected for this proportion. In reality, the cost and disutility impact of ARIA would be even lower than is modelled.

A second scenario analysis is presented in which disutilities are assumed to apply to all AEs, irrespective of severity; in this scenario the values in Table 63 are applied to mild and moderate AEs. This scenario results in a decrease of £[redacted] ([redacted]%) compared with the ICER when only moderate and severe AE disutility was included, to £[redacted]. The associated PAS ICER is in this scenario is £[redacted], a [redacted]% decrease.

Table 63: Adverse event disutility and durations

Adverse event	Disutility	Source	Duration (days)	Source
IRR				
Mild	0	Assumption	N/A	N/A
Moderate	0	Assumption	N/A	N/A
Severe	0.01	Boye et al (2011)	0.125	Eisai LTD. [Data on file] UK clinical expert opinion. 2023
Serious	0.01	Boye et al (2011)	0.125	Eisai LTD. [Data on file] UK clinical expert opinion. 2023
ARIA-E				
Mild	0	Assumption	N/A	N/A
Moderate	0	Assumption	N/A	N/A
Severe	0.0266	Sullivan et al (2006)	6	Eisai LTD. [Data on file] UK clinical expert opinion. 2023
Serious	0.0266	Sullivan et al (2006)	6	Eisai LTD. [Data on file] UK clinical expert opinion. 2023
Isolated ARIA-H				
Mild	0	Assumption	N/A	N/A
Moderate	0	Assumption	N/A	N/A
Severe	0.1	Meckley et al (2010)	6	Eisai LTD. [Data on file] UK clinical expert opinion. 2023
Serious	0.1	Meckley et al (2010)	6	Eisai LTD. [Data on file] UK clinical expert opinion. 2023

B 16. Only grade 3+ AE's that occurred in ≥5% of patients and AE's deemed to be of special interest were included in the economic model. Therefore, only ARIA-E, ARIA-H, and infusion-related reactions were included. Further, to avoid double-counting, only ARIA-H rates and treatment-emergent rates were utilised.

a) Please provide justification for only including grade 3+ AE's. Further, please provide a full overview of adverse events and frequencies from Clarity AD, separated by grade.

Company response: Inclusion of only treatment-related incidence of grade 3+ AEs occurring in ≥5% patients in the trials of the interventions and comparators under consideration is common practice in HTAs, including NICE submissions, as evidenced in three of the ten most recently published NICE technology appraisals.[63–65] Generally AEs below grade 3 are not included in cost-effectiveness analysis due to their limited cost and HRQoL implications.

Table 64 provides a summary of adverse events and frequencies from Clarity AD, separated by severity. There are over 100 separate treatment-related TEAEs

recorded in Clarity AD. Therefore, Table 64 presents an overview of treatment-related TEAEs separated by severity. In Clarity AD, AEs (with the exception of infusion-related reactions) were graded on a three-point scale of mild (discomfort noticed, but no disruption of normal daily activities), moderate (discomfort sufficient to reduce or affect normal daily activities) and severe (incapacitating, with inability to work or perform normal daily activities); rather than CTCAE grade 1, 2, and 3, respectively. Infusion related reactions were graded based on the Common Terminology Criteria for Adverse Events (CTCAE).[66]

Table 64: Overview of treatment-related TEAE separated by severity and TESAE

MedDRA system Organ Class Preferred Term Severity	Number of patients, n (%)	
	Lecanemab (N=897)	Placebo (N=898)
Subjects with any treatment-related TEAE	[redacted]	[redacted]
Mild	[redacted]	[redacted]
Moderate	[redacted]	[redacted]
Severe	[redacted]	[redacted]
Subjects with any treatment-related TESAE	[redacted]	[redacted]

Abbreviations: MedDRA – Medical Dictionary for Regulatory Activities; TEAE – Treatment emergent adverse event; TESAE – Treatment emergent serious adverse event

b) Please provide an updated economic analysis including all grade 3 AE's and all grade 2+ AE's of special interest, irrespective of occurrence rate. In addition, please include all grade 2 AE's that occur in ≥5% of patients.

Company response: As mentioned in the response to part a), ARIA-E, ARIA-H, and infusion-related reactions were included in the economic analysis irrespective of incidence and severity, given these are AEs of special interest (AESIs), thus grade 2+ AESIs are already included.

Overall the majority of TEAEs were mild and moderate in severity. Severe TEAEs were reported for [redacted] placebo patients and [redacted] lecanemab patients in Clarity AD. Severe (Grade 3) AEs of any incidence are provided in Appendix A reproduced from Table 14.3.1.4.1 of the Clarity AD CSR.[2] Only two MedDRA system organ classes (injury, poisoning and procedural complications and nervous system disorders) had >1% patients in either treatment arm. There were more than 200 distinct types of MedDRA preferred term AEs and none of these occurred in >1% patients with severe TEAEs in either treatment arm. Therefore, the

impact of including severe (grade 3) TEAEs on cost-effectiveness is expected to be immaterial. For context, when introducing a hypothetical adverse event with a cost per event of £500 and an incidence of 1% in the lecanemab arm, the base-case list price ICER rises by just [redacted]. Moreover, it is unlikely to be possible to source the necessary disutilities and durations of all events without numerous assumptions which would induce uncertainty.

Therefore, the request to include all grade 3 AE's and all grade 2 AE's that occur in ≥5% of patients has not been implemented in the model.

c) Please provide an updated economic analysis including the associated rates for ARIA-H, ARIA-E, and infusion-related reactions.

Company response: As discussed in the previous responses, ARIA-E, ARIA-H, and infusion-related reactions were included in the economic analysis irrespective of incidence and severity, given these are AEs of special interest (AESIs), thus the CS is already reflective of this request (Document B, Section B.3.3.6, Table 44).

d) Consistent with the request included in the previous adverse event clarification question (CQ B15.), please include disutilities, as well as associated costs, for all requested adverse events.

Company response: As discussed in the previous responses, there were more than 200 distinct MedDRA preferred term AEs, none of these occurred in >1% of patients with severe TEAEs in either treatment arm. Consequently, the inclusion of these adverse events in the analysis is expected to have an immaterial impact on cost-effectiveness and would require numerous assumptions regarding event disutilities and durations which would induce uncertainty; therefore, this has not been conducted in the economic analysis.

Health-related quality of life

B 17. Priority: EQ-5D-5L data from Clarity AD were mapped to EQ-5D-3L index scores using the Hernandez-Alava et al. algorithm to inform patient HRQoL for the MCI due to AD and mild AD health states in the economic model. As the Clarity AD trial did not contain sufficient observations to inform health state

utilities for moderate and severe AD, these were modelled using estimates from published studies.

a) Please describe in detail the procedure used to estimate the health state utility values for the MCI due to AD and mild AD health states based on Clarity AD. Please provide an overview of the data included, the amount of missing data (per arm and time point) and how these missing data were handled. In case regression analysis (e.g. mixed effects modelling) was used, please elaborate on how diagnostics of the regression model were assessed, how the (candidate) covariates as well as interaction terms were selected (with rationale) and how the regression model accounted for nesting effects.

Company response: To generate health state utility values, the mean utility index scores were calculated by corresponding health state e.g. for MCI due to AD, the mean value of EQ-5D was calculated across all observations in which the corresponding health state membership was MCI due to AD. This was performed separately by study arm, including both baseline and post-baseline assessments. Missing data were not imputed. The analysis was not informed by a regression model, therefore no covariate selection or model diagnostics are available.

Table 65 summarises mean patient-reported EQ-5D by selected visit and the number of patients included in each visit.

Table 65: EQ-5D-3L Utility Index Score by selected Visit, subject, ITT (FAS+)

Visit		Placebo (N=875)	Lecanemab (N=859)
Baseline	n	[redacted]	[redacted]
	Mean (SD)	[redacted]	[redacted]
Week 27	n	[redacted]	[redacted]
	Mean (SD)	[redacted]	[redacted]
Week 53	n	[redacted]	[redacted]
	Mean (SD)	[redacted]	[redacted]
Week 79	n	[redacted]	[redacted]
	Mean (SD)	[redacted]	[redacted]

Abbreviations: SD, standard deviation.

b) The resulting utility values for the MCI due to AD and mild AD health states are higher than the UK age and gender matched general population

utilities. Please provide an updated economic model and scenario analysis capping the maximum utility value based on these UK general population utilities (matched based on age and gender).

Company response: This scenario analysis is presented in Clarification scenario analyses – cost-effectiveness results

An overview of scenario analyses results is presented in Table 54. The results are discussed in further detail in response to the respective questions.

Table 54, in which utility values are capped at the age and gender matched general population values. In this scenario, the MCI due to AD health state is capped at the general population value, with all other health states being calculated as relative decrements vs. the previous health state. This scenario results in an [redacted] of £[redacted] ([redacted]%) compared with the corrected base-case list price ICER, to £[redacted]. The associated PAS ICER is in this scenario is £[redacted], an [redacted]% [redacted].

c) Please elaborate on the implications and the benefits and limitations of both approaches (i.e. the utility values higher than the UK age and gender matched general population and the capped utility values).

Company response: Utility values were not capped in the base case in order to align utility data with clinical efficacy data, and to accurately reflect the data from Clarity AD, a large RCT in the population relevant to the decision problem comparing lecanemab vs the comparator of interest in UK clinical practice. Although applying a cap at the age and gender matched general population utility values may provide more face validity, the uncapped values are not outside of the ranges observed in the literature (see response to part d) of this question) and applying a cap does not accurately reflect the HRQoL seen in the trial in patients receiving lecanemab.

d) Please elaborate on how the modelled utility values for the MCI due to AD and mild AD health states based on Clarity AD compare to the reported MCI due to AD and mild AD utility values from the literature (e.g. Coucill et al., Bryan et al., Wimo et al., Ortega et al., Mulhern et al., and Farina at et al.) and provide justification for the observed differences. Please also provide the references for these studies, as all except for Mulhern and Farina were not provided.

Company response: Utility values for the 'MCI' and 'Mild AD' health states are presented in Table 66 for the cited publications. Utility values for the MCI due to AD state were only available from the analysis of Clarity AD. Patient-reported utility values for the mild AD health state from the cited studies ranged from 0.71 to 0.8.

Landeiro et al present a systematic review and meta-analysis of EQ-5D data by stage of AD.[67] The range of self-rated EQ-5D reported for MCI was 0.63-0.89, and

for mild AD was 0.61-0.93. Therefore, whilst estimated values in Clarity AD are relatively high, they are within the ranges reported in the literature.

The reasons for observed differences in EQ-5D between studies are unknown but may be attributable to differences in patient characteristics. The age of patients in some of these studies in general was older than the Clarity AD cohort; for example Farina et al report an age of 80.2 years for patients with mild cognitive impairment, and Mulhern et al report an age of 79.4 years across their cohort, in contrast with the mean baseline age of 71.3 years in Clarity AD. The following Clarity AD exclusion criteria may also induce differences in the population and hence utility estimates compared to the published studies:

- Any neurological condition that may be contributing to cognitive impairment above and beyond that caused by the subject's AD.
- History of transient ischemic attacks (TIA), stroke, or seizures within 12 months of screening.
- Any psychiatric diagnosis or symptoms, (e.g., hallucinations, major depression, or delusions) that could interfere with study procedures in the subject.
- Geriatric Depression Scale (GDS) score greater than or equal to 8 at screening.
- Any immunological disease which is not adequately controlled, or which requires treatment with biologic drugs during the study.
- Subjects with malignant neoplasms within 3 years of screening (except for basal or squamous cell carcinoma in situ of the skin, or localized prostate cancer in male subjects).

The use of EQ-5D-3L scores predicted by the Hernandez-Alava et al algorithm may also contribute to differences when compared to utilities reported from the literature.[68]

Table 66: Utility values for MCI and Mild AD from cited sources

Source	Utility value	
	MCI	Mild AD
Self-rated		
Clarity AD – SoC[2]	[redacted]	[redacted]
Clarity AD – lecanemab[2]	[redacted]	[redacted]
Ortega et al[69]	Not available	0.79
Farina et al[70]	Not available	0.8
Mulhern et al[71]	Not available	0.71
Landeiro et al range[67]	0.63-0.89	0.61-0.93
Patient-by-proxy		
Clarity AD - SoC[2]	[redacted]	[redacted]
Clarity AD - lecanemab[2]	[redacted]	[redacted]
Coucill et al[72]	0.86†	
Bryan et al[73]	0.57†	
Wimo et al[74]	Not available	0.68
Ortega et al[69]	Not available	0.63
Mulhern et al[71]	Not available	0.57
Farina et al[70]	Not available	0.7

†Questionable/mild dementia.
Abbreviations: AD – Alzheimer's disease; MCI – mild cognitive impairment; SOC – standard-of-care

The PDF references for Coucill et al., Bryan et al., Wimo et al. and Ortega et al. were provided within the original CS reference pack, entitled 'Coucill_2001', 'Bryan_2005', 'Wimo_2013' and 'Orgeta_2015', respectively. The company acknowledge a minor spelling error in the title of the PDF for Ortega et al.

e) The modelled utility values in all health states appear to be treatment-dependent (e.g. in the mild AD health state values of [redacted] and [redacted] were used for lecanemab and SoC respectively). Please justify the use of treatment-dependent utility values.

Company response: In Clarity AD, lecanemab was associated with a relative preservation of HRQoL and less increase in caregiver burden, as reported by patients and their care partners, with consistent benefits seen across different scales, within items and subdomains of these scales, and across randomisation strata.[75] At month 18, adjusted mean change from baseline in in EQ-5D-5L and QOL-AD by subject showed 49% and 56% less decline, respectively.[75] QOL-AD by proxy showed 23% less decline.[75]

Differences in utility estimates for lecanemab vs SoC within the same health state may potentially be attributable to differences in disease severity not captured by the CDR-SB health state categorisation alone e.g., a patient with a CDR-SB score of 5 may be expected to have more favourable HRQoL compared with a patient with a CDR-SB score of 9, although both patients would be classified as having mild AD. Comparisons between study arms within health states are however limited by the lack of statistical power to detect these differences.

f) Please provide an updated economic model and scenario analysis using treatment-independent utility values for all health states.

Company response: Results for the requested scenario are presented in Table 54. This scenario results in an increase of £[redacted] ([redacted]%) compared with the corrected base-case list price ICER, to £[redacted]. The associated PAS ICER is in this scenario is £[redacted], a [redacted] increase.

The mean EQ-5D-3L values across both treatment arms were used for the MCI due to AD and mild AD health states (Table 67). Utility values for moderate AD and severe AD were calculated as per the CS base case (Document B, Section B.3.4.4). As discussed in the response to part e) of this question, the company does not consider treatment independent utility values to be appropriate, as this does not capture the differences in quality of life experienced within a health state that are not captured by the CDR-SB health state categorisation.

Table 67: EQ-5D-3L in Each Health State Using CDR-SB Score, ITT (FAS+)

Health state	Parameter	Total
Patient		
MCI due to AD	n	[redacted]
	Mean (SD)	[redacted]
Mild AD	n	[redacted]
	Mean (SD)	[redacted]
Study partner		
MCI due to AD	n	[redacted]
	Mean (SD)	[redacted]
Mild AD	n	[redacted]
	Mean (SD)	[redacted]

Abbreviations: SD, standard deviation.

B 18. The company also included caregiver HRQoL in its economic analysis to capture the associated burden of AD by applying a carer utility decrement to the patient utilities. To capture the impact of patient institutionalisation on the caregiver's HRQoL, a coefficient of -0.09 from Farina et al. was additively applied to the community care utilities in all health states. The currently modelled decrement (-0.09) suggests that institutionalisation of the patient negatively impacts the HRQoL of the caregiver. However, studies of Van Hezik-Wester et al. and Farina et al. reported higher caregiver utilities for severe AD versus moderate AD, which may potentially be explained by a patient institutionalization utility increment (i.e. the caregiver HRQoL may improve when most of the patient care is taken over by an institution). Please further elaborate on the impact of patient institutionalisation on caregiver HRQoL, also providing evidence and expert opinion, and justify the plausibility of the currently modelled decrement.

Company response: Institutionalisation of a loved one can have a significant impact on caregivers of patients with AD, who face feelings of guilt, relief, sadness, or anxiety, a mixture of emotions that can have a serious impact on QoL. Carers may also experience a sense of isolation or loss of identity when their caregiving role diminishes.[76] This is consistent with feedback from clinicians following the July 2023 UK HTA advisory board, with one clinician stating that carers may feel lonely, a sense of guilt, and possibly suffer from depression, and another stating that carers may feel more concerned for their loved one once they have been institutionalised and may not be receiving the same care the that carer was able to give them at home.[55] In addition, carers may continue to experience financial pressures and associated stress upon losing a loved one to an institute.[43]

As stated by the EAG, Van Hezik-Wester et al. report higher caregiver utilities for severe AD versus moderate AD.[77] The question infers that this could reflect an increase in carer QoL when most of the patient care is taken over by an institution. However, in Table 5 of the Van Hezik-Wester publication, it can be seen that caregiver QoL, measured through EQ-5D-5L, decreases from a mean (SD) of 0.832 (0.156) for caregivers of community-dwelling patients to 0.758 (0.260) for caregivers of institutionalised patients, a decrement of 0.074 (n=68).[77] Similarly, although Farina et al. reported higher carer QoL for severe AD compared to moderate AD, the study

also reports a utility decrement of -0.09 (95% CIs: -0.13, 0.03) for caregivers when a patient is institutionalised (n=213).[70] The caregiver utility decrements for patient institutionalisation from van Hezik-Wester et al. and Farina et al. are comparable, thus indicating plausibility of the modelled decrement.

B 19. Proxy utilities were utilised for moderate and severe health states based on one clinician's suggestion to switch to proxy utilities at a moderate AD health state. However, the company also stated that another clinician suggested switching to proxy utilities in the severe AD health state.

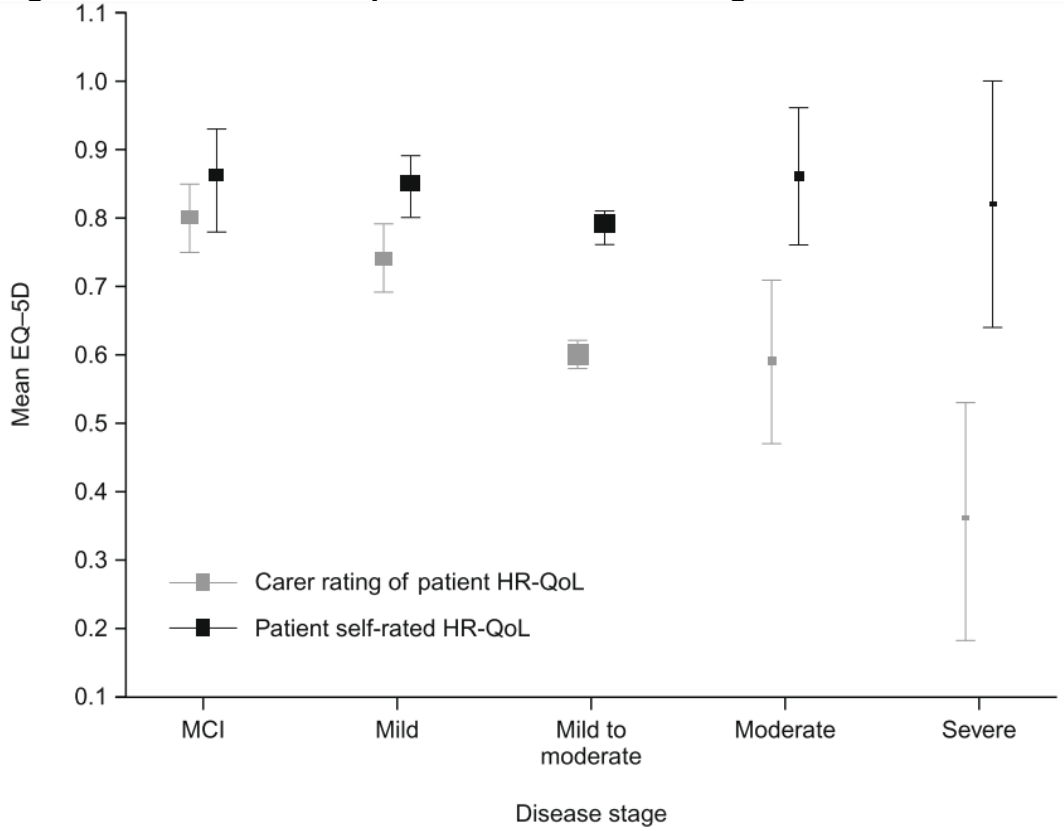
a) Please provide justification as to why the company chose the suggestion of one clinician over the other.

Company response: The company would like to clarify an error in the reference to the July 2023 UK HTA advisory board in the CS; the same clinician stated it would be appropriate to switch to caregiver proxy reported utility values at moderate **or** severe AD.[55] Another clinician stated that caregiver proxy reported utilities should be used at all stages of dementia i.e., for all health states, to supplement any patient-derived value, and that proxy-reported utilities become more important over time as the patient is less able to respond. Other clinicians did not specify at which point they believed it would be appropriate to switch from patient-reported values to caregiver proxy-reported values.[55]

The company considered the second clinician's suggestion to use proxy-caregiver reported utility values across all health to be inappropriate, as doing so would mean disregarding patient-reported data for the MCI due to AD and mild dementia due to AD health states, thus deviating from the NICE reference case.[78] As no consensus regarding the appropriate health state to switch from patient reported utilities to caregiver proxy-reported utilities was reached at a UK HTA advisory board (July 2023), the company considered evidence from a meta-analysis of EQ-5D utility estimates from 48 studies identified via a systematic literature review (SLR), as presented in the CS (Document B, Section B.3.4.4.1; Landeiro et al. 2020).[55] This study found large differences between caregiver proxy-reported and self-reported QoL in patients with AD, with clear divergence at mild to moderate AD and increasing through moderate and severe AD (Figure 21).[79]

The combination of this evidence from Landeiro et al. and feedback from clinicians at the July 2023 UK HTA advisory board, indicating that caregiver-proxy reported utilities would be more appropriate for later stages of AD, informed the company's decision to switch from patient-reported to caregiver-proxy reported HSUVs at moderate AD.

Figure 21: HRQoL in AD patients measured using the EQ-5D



Abbreviations: EQ-5D – EuroQol-5 Dimension; HRQoL – Health-related quality of life
Source: Landeiro et al.[79]

b) Please provide an updated economic model and scenario analysis using proxy utilities for the severe AD health state and patient-reported for the moderate AD health state.

Company response: As discussed in the CS, Document B, Section B.3.4.4, Clarity AD did not contain many observations to inform health state utilities for moderate AD ([redacted] for lecanemab, [redacted] for placebo) due to the small number of patients progressing to moderate AD during the 18-month follow-up period. As such, the patient-reported moderate AD utility values from Clarity AD were not used in this scenario.

Instead, the patient-reported utility for the moderate AD health state (mean [SD]: 0.8 [0.2]) reported by Farina et al. is used. This results in the list price ICER decreasing by £[redacted], to £[redacted] ([redacted]%). The associated PAS ICER is in this scenario is £[redacted], a [redacted]% decrease.

Cost and resource use

B 20. PRIORITY QUESTION Treatment with lecanemab is conditional upon confirmation of Aβ pathology. Diagnostic testing costs are included in the CS base-case for testing with amyloid PET of CSF. However, testing costs are only included for patients treated with lecanemab, thus ignoring costs for testing patients subsequently deemed not to be eligible for lecanemab. 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) Please provide an updated economic model which incorporates diagnostic testing costs for all people eligible for screening into the costs for lecanemab.

Company response: Please see the updated model which incorporates a scenario including diagnostic testing costs for all people screened for Aβ pathology. In order to align with the budget impact analysis conducted for the CS, these costs have been increased in line with the screening failure rate for Aβ positivity in Clarity AD (71.20%, based on 28.80% of patients failing the Tier 5 screening for Aβ pathology).[80] Multiplying the diagnostic testing cost of £305.91 by 1/0.712 results in a total cost of £429.65. This scenario results in an increase/decrease of £[redacted] compared with the corrected base-case list price ICER, to £[redacted]. The associated PAS ICER is in this scenario is £[redacted], a [redacted].

b) Please include a scenario which includes the costs of referral to local services for people that are not amyloid positive.

Company response: Referral to local services would occur for any patient with AD, regardless of whether they are subsequently tested for Aβ pathology. The introduction of testing for Aβ pathology would simply change the stage during the diagnostic pathway at which patients would be referred. As discussed in the CS, Document B, Section B.1.3.6.1, an initial assessment is conducted in a non-specialist primary care setting, during which the patient's history is taken, including basic measurement of cognitive, behavioural, and psychological symptoms, as well as the impact the symptoms have on their daily life.[55,81] Aβ testing will only take place once a patient is referred to a specialist dementia diagnostic service if AD is suspected following physical examination.[55,81] Psychological testing is then conducted to determine if the patient's cognitive impairment is caused by dementia and the correct subtype diagnosis.[55,81]

Following a dementia diagnosis, NHS dementia diagnosis guidance indicates that patients should continue to have check-ups in primary care for ongoing dementia assessment.[82] As such, the costs of referral to local services for people that are not Aβ positive would apply equally to lecanemab and SoC patients hence would not be increased due to the introduction of lecanemab. Therefore, inclusion of such costs would not impact incremental costs and cost-effectiveness, hence this scenario has not been implemented.

B 21. In Clarity AD, *APOE4* carrier assessment was conducted at screening.

a) Is *APOE4* testing expected to be a requirement of the marketing authorisation for lecanemab?

Company response:

[redacted].

b) If not a requirement of the marketing authorisation, what proportion of people are expected to receive *APOE4* tests in UK clinical practice?

Company response: To help answer this question, UK clinical expert feedback was sought. After receiving the responses from the experts, the company identified a typographical error in the question which incorrectly stated

[redacted]

[redacted]

Currently, *APOE4* testing is not routinely conducted in UK clinical practice and is not funded by NHS England, however the company's understanding is that this is under consideration.

Feedback from the experts was that should APOE4 testing become a requirement, this would be offered to all AD patients considered eligible for treatment with lecanemab but it would not be mandatory due to the genetic implications. However, one expert added it should be decoupled from starting therapy and APOE4 testing should be for everyone as part of standard clinical practice. [10,51]

The experts agreed there would be no basis for testing only a proportion of patients and one expert estimated that around 70% would take up the offer of testing. All experts agreed the reason for *APOE4* testing would be to determine a patient's level of risk for ARIA.[83]

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?

Company response: In line with the response to part a), *APOE4* testing is not expected to be a requirement of the marketing authorisation for lecanemab. In addition, as detailed in response to part b), UK clinical experts agreed that if *APOE4* testing were to be offered, this would not be mandatory due to the genetic implications. One clinician stated *APOE4* testing should be for everyone as part of standard clinical practice for risk profiling.[51] As such, these costs would apply to both treatment arms, not exclusively those treated with lecanemab, thus the proposed scenario has not been provided.

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.

Company response: As per the response to part a), we do not expect *APOE4* testing to be a requirement of the marketing authorisation for lecanemab hence we are unable to respond to this question.

B 22. Distribution of patients receiving symptomatic treatments per health state is based on Clarity AD, despite the small number of patients with moderate or severe disease reported in the trial. Further, a proportion of patients receives AChEIs in the MCI due to AD health state (45.7%), despite no pharmacological treatments being recommended in the UK for these patients. Additionally, memantine usage was included for patients with MCI due to AD (9.6%) and mild AD (20.5%), despite memantine only being recommended in the UK for patients with severe AD, or patients with moderate AD who are unable to take AChEIs. These proportions were included to reflect off-label use.

a) Please justify why Clarity AD was used to inform moderate and severe AD health states despite the small patient numbers.

Company response: Clarity AD was used to inform moderate and severe AD health states to align with the pivotal study for lecanemab. The company recognise that the number of patients from Clarity AD informing symptomatic treatment use in moderate AD and severe AD health states is limited (moderate AD: lecanemab, n=75 patients, SoC, n=58 patients; severe AD: lecanemab, n=5 patients, SoC, n=0 patients), therefore scenario analyses are presented in response to parts b) and d) of this question using UK data from the GERAS prospective observational study, reported by Lenox-Smith et al.[84] In each of the alternate scenarios presented, the impact on the ICER is less than [redacted] (Table 54). Due to the immaterial impact of these scenarios, Clarity AD data was retained in the base case. To compare Clarity AD and UK data from GERAS, 85% of mild AD patients in GERAS were receiving symptomatic AD medication at baseline compared to 53% in Clarity AD; only 1% of mild AD patients in GERAS were receiving memantine compared to 21% in Clarity AD.

b) Please provide an updated economic model and scenario analysis informing the distribution of patients receiving symptomatic treatments in the moderate and severe health states from an alternative source.

Company response: A scenario analysis has been conducted in which the proportion of patients receiving AChE inhibitors or memantine in each health state was based on data from the GERAS study, which was identified through hand searching. As described in response to part a, the GERAS study is a prospective observational study which recruited 526 patients from 24 UK centres, reported by Lenox-Smith et al.[84] which was identified through hand searching. In Lennox-Smith et al [84] to align with NICE guidelines on Dementia (NG97), it was assumed no patients with MCI due to AD would receive AChE inhibitors or memantine and no patients with mild AD would receive memantine.[81,84] Table 68 summarises these data.

Results of this scenario are provided in Table 54. This scenario results in a decrease of £[redacted] compared with the corrected base-case list price ICER, to £[redacted]. The associated PAS ICER is in this scenario is £[redacted] a [redacted].

Table 68: Alternative symptomatic treatment use

Parameter	Values	Source
AChE inhibitor		
MCI due to AD	0%	Assumption
Mild AD	84.0%	Lenox-Smith 2016[84]
Moderate AD	81.1%	Lenox-Smith 2016[84]
Severe AD	83.4%	Lenox-Smith 2016[84]
Memantine utilisation		
MCI due to AD	0%	Assumption
Mild AD	0%	Assumption
Moderate AD	3.9%	Lenox-Smith 2016[84]
Severe AD	8.9%	Lenox-Smith 2016[84]

Abbreviations: AD, Alzheimer's Disease; AChE, Acetylcholinesterase.

c) Please provide justification for these proportions being reflective of UK clinical practice.

Company response: Lenox-Smith et al do not report symptomatic treatment use for patients with MCI due to AD, and do not report treatment use by health state as defined by CDR-SB.[84] However, a comparison has been provided of symptomatic treatment use in this study compared with Clarity AD. AChEI inhibitor use in the mild AD and moderate AD health states is higher in Lenox-Smith, but comparable

between the two studies in the severe AD health state. Memantine use is consistently lower across mild-severe AD health states in Lenox-Smith than observed in Clarity AD.

Table 69: Comparison of symptomatic treatment use across health states in Clarity AD vs. Lenox-Smith

Parameter	Clarity AD	Lenox-Smith
AChE inhibitor		
MCI due to AD	[redacted]	0%
Mild AD	[redacted]	84.0%
Moderate AD	[redacted]	81.1%
Severe AD	[redacted]	83.4%
Memantine utilisation		
MCI due to AD	[redacted]	0%
Mild AD	[redacted]	0.5%
Moderate AD	[redacted]	3.9%
Severe AD	[redacted]	8.9%

Abbreviations: AD, Alzheimer's Disease; AChE, Acetylcholinesterase.

Given that GERAS is a study conducted in the UK, and Clarity AD was conducted globally, we recognise that GERAS may be more reflective of current UK clinical practice. However, GERAS did not report symptomatic treatment use for patients with MCI due to AD, which contradicts UK clinical expert feedback that approximately 25% and 10% of patients with MCI due to AD are treated with AChEIs and memantine, respectively, in the UK.[10] In alternate scenarios using these data the cost of symptomatic treatment was varied by ±25%. In the scenario where the cost of symptomatic treatment was increased by 25%, the ICER increased by just £[redacted] compared with the corrected base-case list price ICER, to £[redacted]. The associated PAS ICER is in this scenario is £[redacted], a [redacted] (Table 54). While there are differences in symptomatic treatment usage between Clarity AD and UK clinical practice as per clinician feedback, Clarity AD is broadly representative and matches UK practice closer than the GERAS study. Hence, Clarity AD is considered appropriate for use in the base case.

d) Please provide an updated economic model and scenario analysis with no pharmacological symptomatic treatments for patients in the MCI due to AD health state and no memantine usage for patients in the mild AD health state.

Company response: This scenario results in a decrease of £[redacted] compared with the corrected base-case list price ICER, to £[redacted]. The associated PAS ICER is in this scenario is £[redacted] a [redacted] (Table 54).

B 23. Mean compliance (94.18%) for lecanemab was derived from Clarity AD. Compliance was defined as the (total number of infusions patients actually received) / (total number of infusions the patients could have received), regardless of infusion interruption.

a) Please provide further explanation as to the definition of compliance and provide an overview of the reasons for infusion interruption.

Company response: Compliance was defined in Clarity AD as the (total number of infusions patients actually received) / (total number of infusions the patients could have received). If subjects have infusion interruption (interruption of study treatment) due to TEAE, the number of infusions the patients could have received during TEAE is also counted under total number of infusions the patients could have received.

In Clarity AD, [redacted] ([redacted]%) patients in the lecanemab arm and [redacted] ([redacted]%) in the placebo arm had <100% compliance (i.e., at least one infusion interruption). Of those, [redacted] ([redacted]%) patients in the lecanemab arm and [redacted] ([redacted]%) patients in the placebo arm had infusion interruption (interruption of study treatment) due to TEAE. The remaining patients have infusion interruption (interruption of study treatment) due to missed visits, the reasons other than for COVID-19 were not collected. [redacted] subjects showed good compliance (i.e., [redacted]% subjects had compliance rate ≥75%) in Clarity AD.

b) Please provide supportive evidence to suggest that the utilised compliance rate is likely to be reflective of UK clinical practice, and that non-compliance would plausibly lead to no administration costs?

Company response: To help respond to this question, UK clinical expert opinion was sought as to whether the compliance rate observed in Clarity AD is reflective of anticipated UK clinical practice. Consensus was reached that the rate would be very similar to that observed in Clarity AD, with a very high rate of compliance expected in

clinical practice, although one stated this will need to be confirmed in the real-world setting.[10]

Based on the definition of compliance in Clarity AD (total number of infusions patients actually received) / (total number of infusions the patients could have received), it can be inferred that as a non-compliant patient did not receive the dose, administration did not occur. As such, the administration cost in the model would not be applicable.

c) Please provide an updated economic model and scenario analysis utilising compliance rates in line with current UK clinical practice for AD pharmacological interventions.

Company response: As the only AD pharmacological interventions available in clinical practice in the UK are oral, symptomatic treatments, there are no appropriate analogues for expected compliance for lecanemab, an intravenously administered disease-modifying treatment. As such, no data are available from which to base the proposed scenario, hence this scenario has not been implemented.

d) Please provide an updated economic model and scenario analysis assuming a 100% compliance rate.

Company response: This scenario results in an increase of £[redacted] compared with the corrected base-case list price ICER, to £[redacted]. The associated PAS ICER is in this scenario is £[redacted], a [redacted] (Table 54). It should be noted that this scenario may overestimate the ICER for lecanemab vs SoC as it does not adjust the lecanemab treatment effect, as could be expected with increased compliance.

B 24. Tables 56 and 57 of the CS present the direct medical and non-medical costs, stratified by care setting. The exact inclusion remains unclear to the EAG for these displayed costs.

a) Please provide details and a clear overview of all medical and non-medical costs.

Company response: As discussed in Document B, Section B.3.5.4, direct medical and direct non-medical costs were taken from the Alzheimer's Society Dementia UK

Update (2014), inflated to 2022 prices by an index of 1.14 using the PSSRU NHS Cost Inflation Index.[85,86] The values in the report constitute average healthcare costs per person with dementia, drawing on data from a number of trials and other studies.

The 'direct medical costs' in the model refer to 'healthcare' costs in the report, which cover all primary, community, and secondary care services used. The 'direct non-medical' costs in the model refer to 'social care' costs in the report, which cover public and private costs of assessment and care management, residential care, and home-based community care. The Alzheimer's Society report does not define what 'private costs' are comprised of, nor what proportion of the reported costs are attributable to private care. The direct medical and direct non-medical costs taken directly from the report and the costs used in the model are presented in Table 70 and Table 71, respectively.

Table 70: Annual direct medical costs

Health state	Community		Institution	
	Direct non-medical costs (2013)	Inflated values (2022)	Direct non-medical costs (2013)	Inflated values (2022)
MCI due to AD*	-	£2,704.75	-	£4,428.28
Mild AD	£2,751.00	£3,182.06	£4,504.00	£5,209.74
Moderate AD	£2,695.00	£3,117.29	£9,438.00	£10,916.87
Severe AD	£11,258.00	£13,022.05	£8,689.00	£10,050.50

Abbreviations: AD – Alzheimer's disease; MCI – mild cognitive impairment.
Source: Alzheimer's Society 2014[86] *The ratio of medical care costs between MCI due to AD and mild dementia due to AD are taken from Robinson et al., (2020).[87] MCI costs are 85% of mild dementia due to AD direct medical care costs and 54% of direct non-medical care costs.

Table 71: Annual direct non-medical costs

Health state	Community		Institution	
	Direct non-medical costs (2013)	Inflated values (2022)	Direct non-medical costs (2013)	Inflated values (2022)
MCI due to AD*	-	£1,949.42	-	£28,613.11
Mild AD	£3,121.00	£3,610.04	£24,737.00	£28,613.11
Moderate AD	£7,772.00	£8,989.82	£25,715.00	£29,744.36
Severe AD	£10,321.00	£11,938.23	£25,874.00	£29,928.27

Abbreviations: AD – Alzheimer's disease; MCI – mild cognitive impairment.
Source: Alzheimer's Society 2014[86] *The ratio of medical care costs between MCI due to AD and mild dementia due to AD are taken from Robinson et al., (2020).[87] MCI costs are 85% of mild dementia due to AD direct medical care costs and 54% of direct non-medical care costs.

The Alzheimer's Society report did not report costs for MCI due to AD, nor did any of the papers identified through the SLR. As such, costs for this health state were

derived through a ratio between costs for MCI due to AD and costs for mild AD from a US-based study, Robinson et al. 2020, as described in Document B, Section B.3.5.4.[87] This study reports direct medical and direct non- medical care costs for patients with MCI due to AD and mild AD, as presented in Table 72. The ratios of care costs between these two health states for both medical care costs and non-medical care costs were applied to the mild AD health state costs from the Alzheimer's Society report to derive costs for the MCI due to AD health state.

The company would like to highlight a textual clarification in Section B.3.5.4.1 and B.3.5.4.2 of the CS. The 85% and 54% ratios used to derive costs for the MCI due to AD health state is correct, however the values reported as being used to derive this ratio were incorrect. The correct values are reported in Table 72.

Table 72: Derivation of MCI costs as a proportion of Mild AD costs

Health state	Medical care costs ($)	Non-medical care costs ($)
MCI due to AD (n=677)	1288	359
Mild AD (n=650)	1098	194
Ratio of care costs	0.85	0.54

Abbreviations: AD – Alzheimer's disease; MCI – Mild cognitive impairment
Source: Robinson et al. 2020.[87]

b) Please justify total cost differences between health states and between community vs institution.

Company response: The costs used in the model, presented in response to part a) above, cover the public and private costs of assessment and care management, residential care, and home-based community care. As discussed in the response to part a), the Alzheimer's Society report does not define 'private care', nor report what proportion of costs are attributable to private care. As the severity of AD increases, the costs associated with AD become higher, largely due to the greater need for care and support for individuals at advanced stages of the disease.[88–91] However, as highlighted in the Alzheimer's Society report, costs reported for the institutional setting are often less variable between health states are far less variable in the institutional setting, partly because of the difficulty of identifying per-person differences within full-time care settings, and data typically being reported at the aggregate level.[86]

c) Please elaborate on whether the inclusion of direct non-medical costs is in line with the NICE reference case.

Company response: The direct non-medical costs reported by the Alzheimer's Society comprise public and private costs of assessment and care management, residential care, and home-based community care. As stated in response to parts a) and b), the authors do not define 'private costs', nor do they provide a breakdown of the proportion of costs that are publicly vs. privately funded; thus, it is not possible to exclude private costs from the health state costs. It is therefore possible that the costs are not fully in-line with the NICE reference case, however, it is not possible to estimate the proportion of costs from the Alzheimer's Society report that fall outside of the NICE reference case. As stated in the CS, Document B, Section B.3.5, a suitable alternative to the Alzheimer's Society report to inform health state costs was not identified through the SLR nor through additional hand searches.

To test what the impact of excluding private costs from the health state costs may be, a scenario has been conducted, assuming that 10% of health state costs are attributable to private care, in absence of a defined proportion. As such, all health state costs were reduced by 10% (resulting values reported in Table 73 below), resulting in a list price ICER of £[redacted], an [redacted]

Table 73: Alzheimer's Society cost reduction scenario

Health state	Community		Institution	
	Direct medical	Direct non-medical	Direct medical	Direct non-medical
MCI due to AD	£2,407.57	£1,735.23	£3,941.72	£25,469.22
Mild AD	£2,832.43	£3,213.38	£4,637.32	£25,469.22
Moderate AD	£2,774.77	£8,002.05	£9,717.36	£26,476.16
Severe AD	£11,591.24	£10,626.50	£8,946.19	£26,639.87

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

Results

Scenario and sensitivity analysis

B 25. Please provide a one way sensitivity analysis that includes all the input parameters in the model.

OWSA in which all parameters are varied is presented in Table 74 and Figure 22 using the list price of lecanemab and Table 75 and Figure 23 at the PAS price of lecanemab, showing the 10 most influential parameters in each analysis.

Table 74: Tabulated OWSA results for lecanemab vs SoC, all parameters varied (list price)

Parameter	Lower bound ICER	Upper bound ICER	Range
Time to worsening HR, mild AD (CDR-SB)	[redacted]	[redacted]	[redacted]
Utility: Farina (carer as proxy) - Mild AD	[redacted]	[redacted]	[redacted]
Time to worsening HR, MCI due to AD (CDR-SB)	[redacted]	[redacted]	[redacted]
Utility: Farina (carer as proxy) - Severe AD	[redacted]	[redacted]	[redacted]
Lecanemab compliance	[redacted]	[redacted]	[redacted]
Lecanemab price, 500mg	[redacted]	[redacted]	[redacted]
Utility: Farina (carer as proxy) - Moderate AD	[redacted]	[redacted]	[redacted]
Clarity-AD patient counts at 18 months (CDR-SB), SoC MCI due to AD to MCI due to AD	[redacted]	[redacted]	[redacted]
Discontinuation rate: Clarity, all cause - lecanemab	[redacted]	[redacted]	[redacted]
Clarity-AD patient counts at 18 months (CDR-SB), lecanemab MCI due to AD to MCI due to AD	[redacted]	[redacted]	[redacted]

Abbreviations: AD – Alzheimer's disease; CDR-SB – Clinical dementia rating – sum of boxes; HR, hazard ratio; MCI, mild cognitive impairment; OWSA – One-way sensitivity analysis; SoC – standard of care.

Figure 22: OWSA tornado diagram (list price)

Abbreviations: AD – Alzheimer's disease; CDR-SB – Clinical dementia rating – sum of boxes; HR, hazard ratio; MCI, mild cognitive impairment; OWSA – One-way sensitivity analysis; SoC – standard of care.

Table 75: Tabulated OWSA results for lecanemab vs SoC, all parameters varied (PAS price)

Parameter	Lower bound ICER	Upper bound ICER	Range
Time to worsening HR, mild AD (CDR-SB)	[redacted]	[redacted]	[redacted]
Utility: Farina (carer as proxy) - Mild AD	[redacted]	[redacted]	[redacted]
Time to worsening HR, MCI due to AD (CDR-SB)	[redacted]	[redacted]	[redacted]
Utility: Farina (carer as proxy) - Severe AD	[redacted]	[redacted]	[redacted]
Lecanemab compliance	[redacted]	[redacted]	[redacted]
Lecanemab price, 500mg	[redacted]	[redacted]	[redacted]
Utility: Farina (carer as proxy) - Moderate AD	[redacted]	[redacted]	[redacted]
Clarity-AD patient counts at 18 months (CDR-SB), SoC MCI due to AD to MCI due to AD	[redacted]	[redacted]	[redacted]
Clarity-AD patient counts at 18 months (CDR-SB), lecanemab MCI due to AD to MCI due to AD	[redacted]	[redacted]	[redacted]
Discontinuation rate: Clarity, all cause - lecanemab	[redacted]	[redacted]	[redacted]

Abbreviations: AD – Alzheimer's disease; CDR-SB – Clinical dementia rating – sum of boxes; HR, hazard ratio; MCI, mild cognitive impairment; OWSA – One-way sensitivity analysis; PAS – patient access scheme; SoC – standard of care.

Figure 23: OWSA tornado diagram (PAS price)

Abbreviations: AD – Alzheimer's disease; CDR-SB – Clinical dementia rating – sum of boxes; HR, hazard ratio; MCI, mild cognitive impairment; OWSA – One-way sensitivity analysis; PAS – patient access scheme; SoC – standard of care.

Subgroup analysis

B 26. Please provide subgroup analysis as per the final NICE scope that includes Apoliopprotien E4 (*APOE4*) gene carrier status, MCI due to AD, and mild dementia due to AD.

Company response: Please see the response to Question A9.

Validation

B 27. PRIORITY QUESTION Two advisory boards (held in May and July 2023) are referenced throughout the CS (CS references 61 and 137).

a) Please provide all available information related to these advisory board meetings, including minutes, report as well as presentation slides.

Company response: The July 2023 UK HTA advisory board report and meeting slides will be provided as part of the reference pack for clarification responses. We have responded to clarification question B7a which asks for further clinical validation (supporting evidence) on the generalisability of the baseline characteristics in Clarity AD to the UK population which supersedes CS reference 137 (May 2023 advisory board), therefore it has not been provided.

b) Please provide further information for all other sources of expert opinion used in the CS.

Company response: Other sources of expert opinion used in the CS includes UK clinical validation of adverse event management for ARIA and infusion-related reactions, based on the lecanemab appropriate use recommendations publication for the US (Cummings et al). This has been provided as part of the reference pack for clarification responses.

B 28. PRIORITY QUESTION In CS Tables 71 and 72 a comparison with the CS model and Clarity AD was made with regards to health state occupancy over time. The company stated that "*The model accurately predicts the state occupancy observed in Clarity AD for both treatments. The minor differences, particularly in mortality, may be explained by the use of life tables in combination with AD mortality estimates from published literature.*" According

to the EAG this conclusion is debatable. The differences between the CS model and Clarity AD differ between the health states. For instance, for the "MCI due to AD" health state, the 18-month health state occupancy are almost identical for both treatments while the 18-month health state occupancy for the "Severe AD" health state is substantially overestimated (i.e. estimated to be 18 times and 4 times higher in the model for lecanemab and SoC).

a) Please justify the statement that "The model accurately predicts the state occupancy observed in Clarity AD for both treatments" given the above.

Company response: The company acknowledge that the health state occupancy for the 'Severe AD' state is over-estimated in both the lecanemab and SoC arms of the model compared with the observed occupancy in Clarity AD, however the absolute differences between the modelled and observed occupancy are very small (1.7% and 2.0%, respectively). Moreover, the differences between lecanemab and SoC are relatively consistent between Clarity AD and the model (Table 76); the greatest difference being 2% for the mild AD health state.

Table 76: Health state occupancy at 18 months in Clarity AD and the CEM

		Health state occupancy at 18 months (%)				
		MCI due to AD	**Mild AD**	**Moderate AD**	**Severe AD**	**Death**
Lecanemab	Clarity AD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	CEM					
SoC	Clarity AD					
	CEM					
Difference (lecanemab vs. SoC)	Clarity AD					
	CEM					
Difference in difference (CEM vs. Clarity AD)						

Abbreviations: AD – Alzheimer's disease; CEM – Cost-effectiveness model; MCI – mild cognitive impairment; SOC – standard-of-care

Reasons for the differences between the modelled and observed health state occupancy at 18 months are as follows:

- Mortality in the model is based on life tables in combination with AD mortality estimates from the published literature, to enable UK-specific age-dependency to be incorporated.

- The model uses the pooled baseline health state distribution from both lecanemab and SoC patients (78.8% in the MCI state), while the trial data is based on the treatment-specific baseline health state distributions (79.0% and 78.6% in the MCI state for the lecanemab and SoC arms, respectively).

- In the first 18 months, the following transitions are taken from the published literature[15], and therefore the modelled estimates would not be expected to fully replicate Clarity AD:

    - Moderate AD to mild AD
    - Moderate AD to severe AD
    - Severe AD to moderate AD

b)The abovementioned differences (that differ between health states) cannot be "*explained by the use of life tables in combination with AD mortality estimates from published literature*". Please elaborate on the differences and provide a corrected economic model if applicable.

Company response: Please see the response to part a) above.

B 29. In CS section B.3.14.1 some internal validity checks are discussed.

a) Please provide full details of the internal validity checks performed as well as the results of these checks and potentially actions taken.

Company response:

Table 77 details the internal validity checks that were carried out on the model.

Table 77: Model checklist

Routine checks	Intermittent checks
• All parameters are set to their default values in the control sheet • The model is set to the current agreed base case • The spell check has been run on every sheet • The workbook set up macro has been run	• Model changes have impacted the results in an expected way, e.g. • Changes in costs do not impact QALYs • Disaggregated results are reasonable • There are no obsolete named ranges remaining in the name manager

• The version control sheet has been updated with the new changes and model number • Internal versions go up in increments e.g. 0.1 • External versions go up in whole numbers e.g. 1.0 • State the new ICER, inc. costs and inc. QALYs in the version control sheet • The model version number and date has been updated in the cover sheet • No cells display an error, #REFs or DIV/0 • All distributions for parameters set to 0 are not varied • If a beta distribution is selected then the distributions for parameters set to 1 should also not be varied • All cells are formatted correctly with consistency between inputs and calculated cells • Cell locations have been captured • Sensitivity analysis has been run • All agreed changes from the meetings/emails/phone calls have been implemented • External links have been removed • Models sent out to clients should be saved as 'Read only' versions • Move former versions of the model into the archive folder	• All the drop downs are working and impact the results • All parameters have been added to the control sheet • Logical checks have been conducted, e.g. • Health states add up to 100% • Setting parameters to 0 impacts results • Costs and utilities are linked to the half-cycle corrected health state values • Engines are equal if A1 is set to be the same • All non-relevant data has been removed e.g. personal notes and calculations • All sensitivity analyses display reasonable results • PSA and deterministic results are similar • The model matches the write up • Inputs are correct • All rows have been summed for the full time horizon • All VBA is working correctly • Graph data is labelled correctly and links to the correct source • All labelling is clear

In addition to these, an external independent QC of the CEM was conducted, and validation reports with observations were sent to the model developer to address. The list of checks conducted for the external QC are as follows:

- Model title/version/date appropriate for present submission
- Local data entered appropriately into the model
- Local data source clearly stated in the model
- Product name used appropriately in the model for present submission
- Unit cost data inflated appropriately in the model
- Does any text need adjusted for present submission?
- User selections in the model are appropriate as base case for present submission
- Navigation buttons work
- Navigation buttons are formatted (don't move or change size)
- User controls work (drop-down boxes, combo boxes, tick boxes, etc.)

- All listed options are reasonable for current adaptation
- Is there a restore default button?
- OWSA running function works well
- PSA running function works well
- Named cells are free from non-existent names/ external links
- VBA code refers to named cells/ranges (no absolute cell addresses)
- VBA code refers to the relevant cell
- Color coding is correct for user input cells
- User input cells are unlocked and functioning
- Custom (user defined cells) cells can be restored properly ('Reset base case' command)
- Worksheets have consistent layout
- Worksheet is locked and protected in the appropriate areas (if appropriate)
- Resource unit costs are inflated into the same year value
- Verify all equations using the formula auditing tool (trace dependents of inputs, trace precedents of results)
- Ensure that named ranges and "look ups" have valid and accurate cell references
- Base case results vary as expected under Extreme scenarios (e.g. cost data=0, epi data=0, Market share data, etc.)
- Impact of individual parameters on model results looks reasonable
- Set both treatment and comparator to the same intervention – costs and QALYs should be equal
- Set discount rates at 0% - discounted and undiscounted results should be the same
- Set discount rates at 100% – costs and QALYs should be significantly reduced
- Alter time horizon – total costs and QALYs should increase/decrease reasonably in accordance with longer/shorter durations
- Check that time horizon/cycles/age is linked in correctly in model engine
- Check discounting for costs and outcomes: no discounting for year 1, and annual for subsequent years
- Confirm that the first row of the model engine (e.g. Markov trace if Markov model, occupancy probabilities if PartSA) refers to the correct input
- Confirm that formulas have been copied across correctly
- Confirm that cell-by-cell check was performed in case formulas change (see above)
- Confirm that cost formulas in model engine refer to the right cells
- Confirm that QALYs formulas in model engine refer to the right cells
- Confirm that LY formulas in model engine refer to the right cells
- Confirm that (other outcomes) formulas in model engine refer to the right cells
- Confirm that the model has the cells to check the coherence of Markov states, i.e. the sum of probabilities across Markov states is equal to 100%
- Is OWSA functionality available in the model (for example as a tornado diagram)?

- Is the tornado diagram sorted?
- Does it handle correctly the situations where preference changes all low and high values of the parameter?
- Mean costs and outcomes in PSA are close to the point estimates
- Check distributions (appropriateness of types of distributions) and low and high estimates (95% CI and SE)
- If hazard ratios have been used, check they have been applied correctly

b)Please complete the TECH-VER checklist (Büyükkaramikli et al. 2019, https://pubmed.ncbi.nlm.nih.gov/31705406/) and provide the results.

Company response: Upon reviewing the TECH-VER checklist, the company would like to provide more assurances over the rigour of the model both conceptually and technically. In the development of the economic model, the company has covered the majority of the TECH-VER checklist, as follows:

In ensuring the model received appropriate and sufficient validation, external validation was sought of the model structure, assumptions, and inputs with both UK clinical experts and health economic experts as part of the advisory board.[55] The advisory board report and meeting slides contain details of how model validation was conducted.[55,92]

To ensure technical rigour of the analyses, including avoidance of errors, the model has undergone full internal and external QC. The internal reviewer used the checklist outlined in part a) including tests for extreme values, trace calculations and sensitivity analyses checks, and was in line with health economics best practice. The results of the technical quality check are provided above in part a). The external reviewer checked local data was entered appropriately into the model, checked the sensitivity analyses functioned properly, audited calculation formulas throughout the model, carried out extreme value testing, confirmed the coherence of Markov states, and checked hazard ratios were applied correctly. Additionally, they carried out sense checks such as changing the discount rate, time horizon, and intervention and comparator costs to ensure these had an appropriate impact on the results.

The model checks conducted in the internal and external reviews were comprehensive, and covered of many of the items in the TECH-VER checklist, such as:

1. Model input (pre-analysis) calculations

Calculations that yield direct model inputs from reference source inputs were checked in the data store before they fed through to the rest of the model.

2. Event/state calculations

The Markov trace was confirmed to refer to the correct cells and the coherence of Markov states was checked, i.e., the sum of probabilities across Markov states is equal to 100%.

3. Result calculations

Confirmed that the cost, QALY, and LY formulas in the model engine referred to the correct cells. Confirmed that base case results varied as expected under extreme scenarios (e.g. cost data set to zero, epidemiology data set to zero, market data altered).

4. Uncertainty analysis

Checked the OWSA, probabilistic, and deterministic sensitivity analyses and checked the scenario analyses all operated correctly and produced reasonable results.

5. Overall tests (validation or other supplementary tests)

Ensured the interface, navigation, programming, and data store were all functioning properly. Confirmed the user controls worked, checked the VBA, ensuring it referred to named cells/ranges rather than absolute cell addresses, checked the reset to defaults functionality, and ensured worksheets had a consistent layout. External validation was carried out by comparing results to a range of published AD models from the IPECAD Modelling Workshop, as described in Section B.3.14.3 External validity of the original CS.

Given the large amount of crossover between the checks conducted by the Company and the TECH-VER checklist, the Company do not believe this to be necessary and have therefore not completed the TECH-VER checklist, to allow focus on priority questions within the timeframe for response.

B 30. CS Table 38 provides a comparison with TA217, while CS Tables 73 and 74 provide comparison with the models from the IPECAD modelling challenge (Handels et al., 2022 https://doi.org/10.1002/alz.12811). Although informative, these cross validations are not reflecting all relevant model aspects. Please provide comprehensive cross validations, i.e. comparisons with NICE TA217, the IPECAD models as well as the lecanemab model considered by ICER model (https://icer.org/news-insights/press-releases/icer-publishes-final-evidence-report-on-lecanemab-for-alzheimers-disease/) and elaborate on the identified differences regarding:

a) Model structure and assumptions

Company response: Table 78 presents a comparison of the model structure and associated assumptions utilised in NICE TA217, the IPECAD models, and the lecanemab model considered by ICER (N = 15).[45,93,94] Seven of the 15 models were cohort-transition models, including the current analysis. The remaining eight models were discrete-time microsimulations or discrete-event simulations.

Table 78: Comparison of model structure and assumptions

Model	Model structure	Assumptions
This analysis	*De novo* Markov cohort model Health states based on disease severity and care setting (MCI due to AD, mild AD, moderate AD and severe AD, in the community or in institution, totalling eight model health states plus death.	• One-month cycle length. • Half cycle correction applied. • Backward transitions (to less severe health states) are allowed. • Transitions to death can occur from any health state. • Transition from institutional care back to the community setting are not possible.
TA217[94]	*De novo* Markov cohort model Three health states based on time to institutionalisation (pre-institutionalisation, institutionalisation, and death).	• One-month cycle length. • Half cycle correction applied.
IPECAD[45]	Cohort state-transition model Health states based on disease severity, as defined by: • MMSE: mild = 21-30, moderate = 10-20, severe = 0-9; • FAQ = 0-8, 9-23, 24-30; • NPI-Q = each item≤1, each item≤2, at least one item = 3.	• Annual cycle length. • Half cycle correction applied. • Separate models for MCI and dementia, assumed to be connected with the same underlying progression speed. • MCI dementia progression assumed independent from age • Cognition, function,and behaviour are predictors for one another's next state.
SveDem[35]	Cohort state-transition Health states based on disease severity, as defined by MMSE: mild = 21-30, moderate = 10-20, severe = 0-9.	• Annual cycle length. • Half cycle correction applied.
KP[46]	Cohort state-transition Health states based on disease severity, as defined by MMSE: mild = 18-23, moderate = 10-17, severe = 0-9.	• Annual cycle length. • Half cycle correction not specified. • MCI was assumed to only convert to mild, mild could convert to moderate and severe, and moderate only to severe disease. • No backwards transitions were allowed.
FEM[41]	Dynamic microsimulation Progression reflected by mortality (model does not reflect staging of dementia).	• Two-year cycle length. • Half cycle correction applied to outcomes. • Treatment effect discontinues immediately upon discontinuation.
Herring[42]	Patient-level simulation	• Symptom levels updated and AD dementia diagnostic criteria checked annually.

ADACE[47]	Individual-patient simulation (DICE) Health states based on disease severity, as defined by CDR-SB: mild = 4.5-9.5, moderate = 9.5-16.5, severe = ≥16.5.	• Disease equations evaluated every 6 months, other events (e.g. mortality) on a continuous scale. • Disease progression modelling was decoupled from disease staging.
BASQDEM[27]	Discrete-event simulation Health states based on disease severity, as defined by CDR-SB: mild = 4.5-9.5, moderate/severe = > 9.5.	• Discrete time until mild dementia and moderate dementia. • CDR-SB lineal progression until moderate dementia.
MISCAN[48]	Population-based microsimulation Time-to-event model based on mean dementia duration Four health states: cognitively normal, mild cognitive impairment (MCI), dementia, and death due to dementia (health state definitions not reported in IPECAD publication)	• MCI, dementia, and mortality timings on continuous scale. • No transitions back to previous stages were allowed.
Davis[34]	Cohort state-transition Health states based on disease severity, as defined by Global CDR: mild < 2, moderate = 2, severe = 3.	• Annual cycle length. • Half cycle correction applied. • One singular model for MCI and three Alzheimer's disease dementia states. Age-specific transitions. • Backward transitions (to less severe health states) were not allowed.
CPEC[49]	Cohort state-transition Health states based on disease severity, as defined by MMSE: mild = 21-30, moderate = 10-20, severe 0-9.	• Annual cycle length. • Half cycle correction applied. • Backward transitions (to less severe health states) were not allowed.
Jutkowitz[50]	Microsimulation Health states based on disease severity, as defined by MMSE: mild = > 19, moderates = 19-10, severe = < 10 (only done for this analysis, model include disease stage in these terms).	• One-month cycle length. • Half cycle correction applied. • Mild, moderate, and severe dementia defined only for the cross-model comparisons exercise and based on MMSE thresholds reported in the literature
CEM[43]	Cohort state-transition Health states based on disease severity, as defined by MMSE: mild = 21-26, moderate = 15-20,	• Six-month cycle length. • Half cycle correction not applied. • Treatment effect extrapolated for both cognition and function beyond the initial 18 months as a linear function.

	moderately severe/severe = < 15 (only for baseline severity stratification)	
ICER[93]	Decision analytic model Health states based on disease severity, as defined by CDR-SB, including mild cognitive impairment (MCI) due to AD, mild AD, moderate AD, severe AD, and death.	• Annual cycle length. • Backward transitions (to less severe health states) were allowed. • Transitions to death can occur from any health state. • Transition from institutional care back to the community setting were not possible.

Abbreviations: ADACE – Alzheimer's Disease Archimedes condition event simulator; AD – Alzheimer's Disease; BASQDEM – Basque Discrete-event simulation; CDR – Clinical Dementia Rating; CEM – Cost-effectiveness model; CPEC – Care Policy Evaluation Centre; DICE – Discretely Integrated Condition Event; DMT: Disease-Modifying Treatment; EU: European Union; FAQ: Functional Activities Questionnaire; FEM – Future Elderly Model; HR – Hazard Ratio; HRS – Health and Retirement Study; iADL– Instrumental Activities of Daily Living; IPECAD – International Pharmacoeconomics Collaboration Alzheimer's Disease; IWG – International Working Group; KP – Kungsholmen Project; MCI – Mild Cognitive Impairment; MISCAN – MIcrosimulation SCreening ANalysiS; MRI – Magnetic Resonance Imaging; NACC – National Alzheimer's Coordinating Center; NIA-AA – National Institute on Aging-Alzheimer's Association; NINCDS-ADRDA – National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association; NPI – Neuropsychiatric Inventory; PET – Positron Emission Tomography; QALY – Quality-Adjusted Life Year; RR – Relative Risk; SD – Standard Deviation; SveDem – Swedish Dementia Registry; TICS – Telephone Interview for Cognitive Status; US – United States.

b) Input parameters related to:

i. Clinical effectiveness

ii. Health state utility values

iii. Resource use and costs

Company response: Table 79 presents a comparison of the clinical effectiveness, HSUVs, and resource use and cost data from the various models. Resource use and cost data for the SveDem, KP, FEM, Herring, ADACE, BASQDEM, MISCAN, Davis, CPEC, Jutkowitz, and CEM models was not reported in the IPECAD paper and individual publications have not been searched due to time constraints.[27,34,35,41–43,45–50]

Table 79: Comparison of clinical effectiveness, HSUVs, resource use, and costs

Model	Clinical effectiveness	HSUVs	Resource use and costs
This analysis	Transition probabilities for the first 18 months of the analysis were calculated from the baseline and 18-month distributions of patients across each health state based on CDR-SB as observed in Clarity AD. Beyond 18-months, transition probabilities were estimated from Potashman et al.[95]	Clarity AD, Farina et al., 2020[70], and Black et al. 2018.[96]	NHS reference costs, BNF, PSSRU, HCHS
TA217[94]	Focused on delay in time-to-institutionalisation since interventions are symptomatic.	Jönsson et al, 2006[97]	NHS reference costs, PSSRU (latest available), Dementia UK report 2007
IPECAD[45]	MCI to AD-dementia rate was multiplied with 0.70.	Neumann et al.[98] MCI: 0.73 Mild: 0.69 Moderate: 0.53 Severe: 0.38	Costs of care per year (Gustavsson et al. 2011[99]) MCI: $13,364 (assumed 50% of mild AD) Mild: $26,727 Moderate: $31,644 Severe: $40,645 Institution-mild/moderate: $111,902 Institution-severe: $113,523
SveDem[35]	MCI to AD-dementia rate was multiplied with 0.70.	N/R	N/R
KP[46]	MCI to AD-dementia rate was multiplied with 0.70.	N/R	N/R
FEM[41]	MCI to AD-dementia rate was multiplied with 0.70.	N/R	N/R

Herring[42]	30% reduction in annual rates of change for MMSE, NPI, and DAD.	N/R	N/R
ADACE[47]	Amyloid level calibrated to obtain 30% reduction in AD conversion rate in 2 years.	N/R	N/R
BASQDEM[27]	Time from MCI to mild or moderate dementia multiplied by 1.3.	N/R	N/R
MISCAN[48]	MCI duration prolonged with 30% of treatment duration.	N/R	N/R
Davis[34]	Transition rates from MCI to each of AD-dementia states multiplied by 0.70.	N/R	N/R
CPEC[49]	MCI to AD dementia rate was multiplied by 0.70.	N/R	N/R
Jutkowitz[50]	30% reduction in 5-year proportion of transitioning to moderate dementia.	N/R	N/R
CEM[43]	30% reduction in change in MMSE and ADL over 18 months.	N/R	N/R
ICER[93]	HR of 0.69 applied to MCI due to AD and mild AD health states when transitioning to more severe health states. HR of 1.00 applied to moderate AD and severe AD.	**Patient** / **Community** / **Long-term** MCI due to AD / -0.17 / -0.17 Mild AD / -0.22 / -0.19 Moderate AD / -0.36 / -0.42 Severe AD / -0.53 / -0.59 **Caregiver** / **Community** / **Long-term** MCI due to AD / -0.03 / -0.03 Mild AD / -0.05 / -0.05 Moderate AD / -0.08 / -0.08 Severe AD / -0.10 / -0.10	Annual wholesale acquisition cost: $26,500 MRI unit cost: $261 Annual cost of long-term care: $88,728

Abbreviations: ADACE – Alzheimer's Disease Archimedes condition event simulator; AD – Alzheimer's Disease; ADL – Activities of Daily Living; BASQDEM – Basque Discrete-event simulation; BNF – British National Formulary; CDR-SB – Clinical Dementia Rating Scale Sum of Boxes; CEM – Cost-effectiveness model; CPEC – Care Policy

Evaluation Centre; DAD – Disability Assessment for Dementia; FEM – Future Elderly Model; HCHS – Hospital and Community Health Services; HR – Hazard Ratio; IPECAD – International Pharmacoeconomics Collaboration Alzheimer's Disease; KP – Kungsholmen Project; MCI – Mild Cognitive Impairment; MISCAN – MIcrosimulation SCreening ANalysiS; MMSE – Mini-Mental State Examination; MRI – Magnetic Resonance Imaging; NHS – National Health Service; NPI – Neuropsychiatric Inventory; N/R – Not Reported; PSSRU – Personal Social Services Research Unit; SveDem – Swedish Dementia Registry.

c) Estimated (disaggregated) outcomes per comparator/ intervention

i. Life years

ii. QALYs

iii. Costs

Company response: As concluded by Handels et al., there is wide variation in inputs for costs and HRQoL weights that varied in setting and/or perspective. As such, outcomes and results relating to costs, QALYs, and ICERs were considered insufficiently compatible and have not been presented here.

B 31. CS Tables 73 and 74 provide a comparison of duration of state occupancy (years) compared with the IPECAD modelling challenge models. The company stated that "*Overall, this economic analysis shows comparable results to other published models, particularly those with comparable settings*". According to the EAG this conclusion is debatable.

a) In CS Table 73, it becomes apparent from the models that included the "severe AD" health state, Mild AD is commonly the health state with the second longest duration of occupancy, while only for the CS model the health state with the second longest duration of occupancy was the "severe AD" health state. More specifically, occupancy in the "severe AD" health state was 23% in the company's analysis while for the other models this ranged between 2%-11%.

i. Please explain this relatively large discrepancy between the CS model and the IPECAD models

ii. Given the above, please justify the conclusion "Overall, this economic analysis shows comparable results to other published models, particularly those with comparable settings".

Company response: The cause of differences in health state occupancy between models is not fully known. However, the rate of mortality is expected be a key determinant of time spent in the severe AD state. When using mortality data from

Potashman et al. (see response to question B9 part f), the proportion and duration of time spent in each state is more consistent with published models (Table 80 and Table 81). The time spent in each health state is similar between the updated company base case using mortality data from Potashman et al and the CPEC and Davis models. The CPEC model was commissioned by ARUK and developed by the PSSRU at LSE with NICE requirements in mind, and therefore represents a very similar setting to the current submission. The Davis model used the NACC database for natural history data and also defined health states based on CDR-SB, in line with the Company's model. The choice of mortality data may therefore explain some of the observed differences.

Table 80: Duration of state occupancy, MCI starting state

	Duration of state occupancy (years)			
Model	**MCI due to AD**	**Mild AD**	**Moderate AD**	**Severe AD**
CPEC[100]	3.63	3.23	1.14	0.54
Davis[34],	3.38	2.97	0.99	0.73
MISCAN[48]	3.46	5.99		
BASQDEM [27]	4.46	2.88	0.36	
ADACE[47]	4.61	1.98	0.73	0.18
Herring[101]	3.52	4.24		
FEM[102]	5.54	2.16		
KP[46]	3.71	1.70	0.54	0.72
SveDem[35]	3.68	2.67	2.02	0.38
IPECAD[26]	4.77	0.97	1.50	0.65
Company submission	[redacted]	[redacted]	[redacted]	[redacted]
Updated company base case	[redacted]	[redacted]	[redacted]	[redacted]
Updated company base case + mortality data from Potashman	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AD, Alzheimer's disease

Table 81: % state occupancy, MCI starting state

	%			
Model	MCI due to AD	Mild AD	Moderate AD	Severe AD
CPEC[100]	43%	38%	13%	6%
Davis[34],	42%	37%	12%	9%
MISCAN[48]	37%	63%		
BASQDEM[27]	58%	37%	5%	
ADACE[47]	61%	26%	10%	2%
Herring[101]	45%	55%		
FEM[102]	72%	28%		
KP[46]	56%	25%	8%	11%
SveDem[35]	42%	31%	23%	4%
IPECAD[26]	60%	12%	19%	8%
Company submission	[redacted]	[redacted]	[redacted]	[redacted]
Updated company base case	[redacted]	[redacted]	[redacted]	[redacted]
Updated company base case + mortality data from Potashman	[redacted]	[redacted]	[redacted]	[redacted]

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

b) Also from CS Table 73, it becomes apparent that the current model has the longest duration of occupancy in the "severe AD" health state (37% versus 17%-32%)

i. Please explain this relatively large discrepancy between the CS model and the IPECAD models

ii. Given the above, please justify the conclusion "Overall, this economic analysis shows comparable results to other published models, particularly those with comparable settings".

Company response: As for Question B31a, when using mortality data from Potashman et al. (see response to question B9f), the proportion of time spent in each state is more consistent with published models (Table 82 and Table 83). The time spent in each health state is similar between the updated company base case using mortality data from Potashman et al. and the CPEC and ADACE models. The ADACE model is US-based and uses ADNI data but does use probability of institutionalisation data from a UK-based study. The CPEC model was

commissioned by ARUK and developed by the PSSRU at LSE with NICE requirements in mind, and therefore represents a very similar setting to the current submission.

The time spent in each health state is less similar to the model developed by Jutkowitz et al, but this was a US-based model that modelled a much older patient population (mean age of 83 years at diagnosis) and is therefore less comparable to the CS.

Table 82: Duration of state occupancy, Mild AD starting state

	Mild AD	**Moderate AD**	**Severe AD**
CPEC[100]	4.25	2.03	1.36
CEM[43]	7.86		
ADACE [47]	2.75	1.70	0.94
Jutkowitz[50]	1.44	2.49	1.85
Company submission	[redacted]	[redacted]	[redacted]
Updated company base case	[redacted]	[redacted]	[redacted]
Updated company base case + mortality data from Potashman	[redacted]	[redacted]	[redacted]

Abbreviations: AD – Alzheimer's disease

Table 83: % state occupancy, Mild AD starting state

	Mild AD	**Moderate AD**	**Severe AD**
CPEC[100]	56%	27%	18%
CEM[43]	100%		
ADACE [47]	51%	32%	17%
Jutkowitz[50]	25%	43%	32%
Company submission	[redacted]	[redacted]	[redacted]
Updated company base case	[redacted]	[redacted]	[redacted]
Updated company base case + mortality data from Potashman	[redacted]	[redacted]	[redacted]

Abbreviations: AD – Alzheimer's disease

Section C: Textual clarification and additional points

C 1. Please provide a copy of reference 137 cited in document B of the CS: Eisai. AD Advisory Board, Hilton Belfast ABN - 9th May 2023. 2023.

Company response: Please see the response to Question B27.

C 2. Please provide a copy of reference 138 cited in document B of the CS: EISAI. [Data on file] Clinical efficacy. DOF-01. 2023.

Company response: This will be provided as part of the reference pack for clarification responses.

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NICE National Institute for Health and Care Excellence

Single Technology Appraisal

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

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	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 no funding from the company or any of the comparator treatment companies in the last 12 months. Several projects under the Dementia Consortium umbrella, funded in early 2022, are either ongoing or have been recently terminated. The Dementia Consortium brings together experts in target biology from academia and drug discovery experts from industry. The project provides funding and in-kind support for research projects typically 2 to 3 years in duration. Alzheimer's Research UK and the Dementia Consortium Industry partners, which includes Eisai, share the cost and risk of early-stage dementia drug discovery. **VAPB: ER-mitochondria signalling as a new target for Dementia (VAPB-PTPIP51 tethering)** • Status: Ongoing • Funding: Eisai provided £148,272.07, invoice dated 10 March 2022 **C9ORF72: Identification of tool compounds targeting the SRSF1-dependent nuclear export of pathological C9ORF72-repeat transcripts** • Status: Project terminated after funding partners decision meeting in May 2023 • Funding: ○ Eisai provided £28,588.86, invoice dated 1 October 2022

	○ Takeda provided £23,270.10, invoice dated 31 August 2022 **Kings/ALS: Validating new promising drug targets in Amyotrophic Lateral Sclerosis** • Status: Ongoing, the whole project was paid upfront by all partners • Funding: Takeda provided £97,377.90, invoice dated 11 November 2022
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?	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 in the dementia field. 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 to 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 and care available on the NHS?	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 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 people 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. With an ageing population, current projections anticipate that prevalence of dementia could rise to 1.1 million by 2030.[xiii] There is huge unmet need for a treatment that could slow down progression of disease 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) 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 and may stop symptoms from getting worse. *"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. 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 lecanemab 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)*

Advantages of the technology

9. What do patients or carers think are the advantages of the technology?	We spoke to several individuals who received lecanemab in a trial setting. They expressed mixed opinions regarding its benefits. Patient 1 **has experienced notable stability in his memory over three years since being on the drug**. The patient appeared to have joined the trial at a very early stage of their disease progression, where they still maintained independence in most of their daily activities. He maintains an active lifestyle, engaging in cycling and swimming regularly, and maintains a disciplined diet. According to the patient and his wife, this regimen, combined with lecanemab treatment, has significantly slowed the progression of memory loss, with the patient's memory staying at a consistent level and showing no significant

deterioration. This outcome is seen by the patient as “uplifting”, despite occasional minor lapses, such as repetitive conversations or asking the same questions multiple times a day.

> *“…seeing the difference between [Patient 1]’s journey and my sister’s journey [who also has Alzheimer’s] has just been miraculous really. I feel so grateful that [Patient 1] is as well he is. He carries on with his normal activities, he does all his sport, he is very social”,* - wife of Patient 1, who participated in the lecanemab clinical trial and is currently on the extension.

> *“…if you had to evaluate that as opposed to the normal route of people who have memory loss… I mean he is living his own life really… It’s given us so much extra time together where we are doing things together and enjoying each other and you can’t really put a price on that*”, - wife of the Patient 1, who participated in the lecanemab clinical trial and is currently on the extension.

The carer for Patient 2 initially did not notice any discernible effect on her husband's condition while he was participating in the lecanemab trial. It was **only after he discontinued his involvement in the trial that she observed a significant acceleration in the rate of his cognitive decline**. The carer expressed a revised perspective, indicating that in her view her husband would have experienced a faster decline had he not been on the drug.

> “*He was actually on lecanemab but … the lead doctor thought he was on the placebo. I thought he was on the placebo because he still seemed to be declining and he had absolutely no side effects. However, when he came off lecanemab, he fell off a cliff - he has been falling much faster since the drug was withdrawn. … So, having thought that it hasn’t made any difference, I’ve now changed my view – I think he would have declined much quicker had he not been on the drug*”, - carer for Patient 2, who participated in the lecanemab clinical trial.

The carer for Patient 3 **remained sceptical about the treatment's overall effectiveness**. The carer reported that her husband did not notice any notable effects from the drug during its use, and she witnessed a steady, gradual decline in his condition.

> *“[Patient 3] doesn’t feel he was on the drug. I certainly have noticed nothing other than a similar very gradual declining. I don’t feel there was any slowing down of the decline and then speeding after he stopped*”, - carer for Patient 3, who participated in the lecanemab clinical trial.

In the conversations, it was clear that Patients 2 and 3 are at a later stage of progression than Patient 1.

> *“[Patient 3] has days when his thinking is clearer than others. And he does sometimes say: ‘why would anybody want to lengthen this miserable period of their life?’ And I say ‘if it slows down any deterioration’… ‘yes, but you’d have to catch it so early that people would still having a good quality of life. And then on another day he can’t even process those thoughts because he is quite happy in his little world: he’s safe, he’s looked after, he doesn’t look towards the*

	future at all, he certainly doesn't have look towards the past, he lives in the present five to ten minutes. So, it is very difficult to know about this", - carer for Patient 3, who participated in the lecanemab clinical trial. The carer for Patient 3 expressed the view that any potential advantages of the drug might be most apparent with an exceptionally early diagnosis when the individual still maintained a reasonable quality of life. Intervening later, she believed, could merely prolong a period of distress without offering substantial improvements. "*You would have to catch it so early to slow down the deterioration so for it to be valuable to that person and the people around them. It may sound very selfish but I'm now looking at a possibly lengthy future where the degradation of my quality of life has been severely affected. Let alone the quality of [Patient 3]'s life. … why on Earth would I want this extended? … Although I don't want [Patient 3] dead, I don't see a great deal of positive in lengthening what he's going through*", - carer for Patient 3, who participated in lecanemab clinical trial. These varying experiences may suggest that lecanemab works best when it is used as early in the disease as possible.

Disadvantages of the technology

10. What do patients or carers think are the disadvantages of the technology?	Participants in the lecanemab trial (and their carers) reported several challenges and disadvantages associated with the drug. These issues ranged from difficulties during the infusion process, concerns about medical equipment and staff expertise, to the experiences with MRI and PET scans. Additionally, one patient initially on a placebo, who got the drug via extension label experienced small brain bleeds, leading to concerns about the medication's safety and effectiveness. **Infusion Process Experiences** The drug is 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 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 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. "*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. One person described the process of PET scans as somewhat burdensome, especially due to the extended time on the trolley after the tracer administration. "*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. **Brain bleedings** One patient who initially was on placebo experienced small brain bleeds after a few infusions on the extension label. "*There were not big bleeds, they were small spots, but they were increasing, and we were worrying that if he got anymore, it could have let him to having a stroke or something like that. That's when they suggested he should come off it*", - carer for Patient 3, who participated in the lecanemab clinical trial. **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 a piece of research to understand the trade-offs people were willing to make between the benefits and risks of hypothetical treatments for Alzheimer's disease.[xiv] University Medical Center Groningen explored the highest level of risk people would accept in exchange for delaying the progression of Alzheimer's Disease to a more severe stage by two years. Among over 3,600 people in the UK 15% of respondents reported living with memory problems. What we learned:
	• 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 and poorer quality of life:
	  ○ 1 in 2 people were willing to accept up to a 10% risk of severe side-effects.
	  ○ 1 in 4 people were willing to accept a greater than 50% risk of moderate side-effects.
	• People were more likely to accept higher levels of risk in a new treatment if they were young, male, highly educated and lived alone.
	• Individuals who hold positive beliefs regarding the benefits of medicines are more willing to accept higher risks. On the other hand, those who have negative views about the potential harm and overuse of medicines tend to be more cautious and prefer lower risks.

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 would be expected that, if given a license, the label would indicate that the drug would be suitable for those with mild cognitive impairment (MCI), or for those in the mild stage of Alzheimer's disease, with confirmed amyloid positivity. • Alzheimer's Research UK acknowledges the recent scope update by NICE, which now includes 'ApoE4 carrier status' as a subgroup. It's worth noting that the NHS currently does not routinely provide tests for APOE genes. At present, there is a lack of evaluations conducted on the costs and scale of implementing such testing within the NHS. • Given challenges around MRI and pacemakers[xv] this will be a specific issue which will need further evaluation. This issue was reflected in the conversations we had with trial participants. • Authors of a recent Viewpoint in JAMA Neurology noted that the supplement for the lecanemab trial publication "revealed noteworthy sex differences". Although the trial found that, overall, lecanemab delayed progression by 27%, the difference between the treated and placebo groups was 43% in men and only 12% in women.[xvi] This discussion indicates a potential area requiring deeper investigation.

	• The early-onset population could experience greater benefits of 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 experiences, and we are including it in the submission.

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.[xvii] It is unlikely that services across the UK will be uniformly ready to treat and manage patients on lecanemab if and when it becomes available. • 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. • Discussion of equality issues relating to the target condition should include the consideration that there is higher prevalence of dementia in women,[xviii] and over 60% of dementia carers are women.[xix] • Findings from the Dementia Attitudes Monitor in 2018 showed that people from black, Asian and minority ethnic (BAME) backgrounds are more likely to agree that 'dementia is an inevitable part of ageing'. Survey results also indicated that those from social grades DE (semi-skilled and unskilled manual workers, and those with no formal qualifications, state pensioners, casual and lowest grade workers, unemployed with state benefits only) were also more likely to agree with the statement.[xx] BAME communities are also less likely to get a diagnosis.[xxi] Less understanding and awareness of the diseases that cause dementia within particular communities could result in people being less likely to come forward to seek treatment. • The lifetime risk of Alzheimer's disease in people with Down's syndrome is more than 90%,[xxii] and is the leading cause of death in this population.[xxiii] 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.[xxiv] 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 lecanemab. From the patient perspective it is crucial to avoid immediate negative reactions solely due to complexities in lecanemab implementation. ▪ The full benefits of lecanemab may become more evident in the long-term, particularly as greater care costs are associated with the later, moderate to severe stages of dementia, and will prove challenging to evaluate as the Phase III trial only covered eighteen months in a carefully curated population. It is important that a neutral approach to this uncertainty is taken given the potential benefits and high unmet need (acknowledging 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. Approval of the drug would also bring about a major step change in the current care pathway to enable consistent outcomes evaluation and monitoring, requiring resource to both address insufficient infrastructure capacity and to train and upskill clinicians. ▪ The collaborative effort between MHRA, NICE, NHS 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. Data collection agreement should be developed jointly with patient groups and reflect safety profile and long-term outcomes of the treatment, including but not limited to expected duration of treatment and stopping criteria. 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.[xxv] 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. The historic underinvestment in diagnostic infrastructure 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 may not be equitable to include the costs of diagnostics solely for the first in class drug 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.[xxvi] 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.[xxvii] Similarly, CSF has limited current use in the diagnosis of Alzheimer's disease.[xxviii] ▪ Multiple MRI scans will likely be required for monitoring of Amyloid Related Imaging Abnormalities (ARIA). Appropriate Use Recommendations (AURs) developed to assist in guiding the use of new agents such as lecanemab into clinical practice recommend obtaining MRIs within 1 year prior to initiation of treatment, prior to the 5th, 7th, 14th infusions and an additional week 52 MRI scan, especially for APOE4 genotype carriers and those with evidence of ARIA on earlier MRIs.[xxix] ▪ 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.[xxx] 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. <u>Patient preferences and outcomes</u> • 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.[xxxi] These are not included in the Clinical Dementia Rating Scale (CDR) which clinicians and researchers employ to evaluate the severity of dementia. It is vitally important that HTA bodies consider the outcomes that matter to people with Alzheimer's disease when assessing new medicines. <u>Wider societal benefit</u> ▪ NICE should use existing flexibilities to include relevant wider societal benefit in the lecanemab evaluation. NICE has previously considered wider impacts in specific evaluations such as nalmafene[xxxii] 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 lecanemab 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[xxxiii]. 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[xxxiv]. 60% of people receiving home-care services are living with dementia[xxxv]. In England and Wales, the number of people living with dementia who need palliative care will almost quadruple by 2040[xxxvi]. Carer quality of life ▪ 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). However, Eisai raised concern that substantial added benefit generated by lecanemab may not be captured within the existing QALY framework due to the use of EQ-5D to estimate caregiver HRQoL. The company noted that the EQ-5D may not sufficiently capture these effects as it was not designed for use on caregivers and focusses on physical health[xxxvii] and suggested alternative measures specifically designed to assess caregiver burden, such as Zarit's Burden Interview (ZBI) to capture the impact of caring for a person with AD more accurately. ▪ We urge NICE to consider incorporating alternative assessments of carer quality of life beyond the existing framework. If such consideration lies beyond a Single Technology Appraisal, 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[xxxviii].

Key messages

14. In up to 5 bullet points, please summarise the key messages of your submission.	• There is undoubted unmet need for a treatment that could slow down progression of Alzheimer's disease. • Approval of lecanemab 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 lecanemab 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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NICE National Institute for Health and Care Excellence

Single Technology Appraisal

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

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 lecanemab 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 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. We 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 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. 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 were able to speak with one person who participated in the lecanemab trial. Their comments are indicated as such.

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 dementia 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. Dementia 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[1]. 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]. Dementia also progressively limits people's ability to carry out daily activities and hobbies outside of the house. By the middle stages of dementia, 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 dementia 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].

	'I am glad I'm still able to function i.e. going shopping and working, though it's getting tough. I am getting the feeling of being followed by something - it gets worse especially when using the lifts at work and in a store – I get into the lift, the door shuts and after a little while it opens again for no reason. It only happens to me but not my colleagues etc. Am I losing it or something strange is going on?' [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[2]. 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[3], and that 60% of people who draw on support from homecare are people with dementia[4]. '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].

[1] https://www.alzheimers.org.uk/sites/default/files/2022-07/left-to-cope-alone-after-diagnosis-report.pdf
[2] https://www.alzheimers.org.uk/about-dementia/symptoms-and-diagnosis/how-dementia-progresses/changes-in-behaviour-later-stages
[3] The cost of dementia in England, Wittenberg et al 2018
[4] 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 that an individual's health and wellbeing[5]. 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[6]. 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[7]. 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[8], 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[9].

[5] https://www.alzheimers.org.uk/sites/default/files/2022-09/APPG%20on%20Dementia%20Workforce%20Matters%20Report%202022.pdf
[6] https://www.alzheimers.org.uk/about-us/dementia-UK-leading-cause-of-death
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[8] https://www.alzheimers.org.uk/sites/default/files/2022-07/left-to-cope-alone-after-diagnosis-report.pdf
[9] 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[10].

[10] 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?	Our survey and focus group 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 survey, 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)[11][12]. 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.

[11] https://www.alzheimers.org.uk/about-dementia/types-dementia/treatment-support-alzheimers-disease#content-start
[12] 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[13] and Northern Ireland[14] and half of people with dementia in Wales don't have a diagnosis[15.] This is despite 91% of people saying that they benefitted from receiving one[16.] 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[17]. 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[18], 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[19,] 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[20]. 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[21]. 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[22].

	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[23]. 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[24]. 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)[25]. 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[26]. The workforce is also over-stretched, with vacancies at 152,000[27].

[13] https://digital.nhs.uk/data-and-information/publications/statistical/primary-care-dementia-data/october-2023
[14] https://www.health-ni.gov.uk/sites/default/files/publications/health/rdp-ni-2023.pdf
[15] https://www.gov.wales/sites/default/files/publications/2019-04/dementia-action-plan-for-wales.pdf
[16] https://www.alzheimers.org.uk/news/2022-05-16/91-people-affected-dementia-see-clear-benefits-getting-diagnosis
[17] https://www.alzheimers.org.uk/sites/default/files/2022-07/left-to-cope-alone-after-diagnosis-report.pdf
[18] 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)
[19] https://www.nice.org.uk/guidance/ng97
[20] 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
[21] https://digital.nhs.uk/data-and-information/publications/statistical/primary-care-dementia-data/october-2023
[22] . 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)
[23] https://www.alzheimers.org.uk/sites/default/files/2022-07/left-to-cope-alone-after-diagnosis-report.pdf
[24] https://www.alzheimers.org.uk/about-us/policy-and-influencing/dementia-true-cost-fixing-care-crisis
[25] https://onlinelibrary.wiley.com/doi/full/10.1002/gps.5113
[26] https://www.alzheimers.org.uk/sites/default/files/2022-09/APPG%20on%20Dementia%20Workforce%20Matters%20Report%202022.pdf
[27] 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?	The following responses are from people living with Alzheimer's disease who do not have direct experience of lecanemab. The most frequently cited advantage of lecanemab, 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] We were able to speak with one person who participated in the lecanemab trial. They commented on the advantages: 'The advantage of lecanemab for me, as a person with Alzheimer's disease, is that it holds back the symptoms and is giving me more time to enjoy my life.'

Disadvantages of the technology

10. What do patients or carers think are the disadvantages of the technology?	The following responses are from people living with Alzheimer's disease who do not have direct experience of lecanemab. 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. '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]'. We were able to speak with one person who participated in the lecanemab trial. They commented on the disadvantages: 'The only disadvantage of lecanemab is that it is not a total cure for the disease.'

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 lecanemab in some populations (including a gender difference), but this relates to clinical effectiveness. We have no evidence to add from the experiences of people with dementia and carers.

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 lecanemab relies on an accurate diagnosis, and there are inequalities in access to diagnosis. People living in deprived areas, people living in rural areas, and people from ethnic minority backgrounds are less likely to have a diagnosis[28]. There is also regional variation in diagnosis rates, with diagnosis rates in local authorities ranging from around 50% to around 90%[29]. Every effort needs to be made to reduce the likelihood of regional variation in access to DMTs. While the lecanemab clinical trial study did include some participants from ethnic minority backgrounds, within this category some ethnic backgrounds only made up a very small proportion of all participants. As such, it could be argued that we don't fully understand the effectiveness of lecanemab in all minority ethnic groups. People with Down Syndrome are more likely to develop Alzheimer's disease and will have amyloid clumps in their brains by the age of 40[3031]. Due to the age cut-offs of clinical trials it is unlikely that many (if any) people with Alzheimer's disease and Down Syndrome were enrolled on the trial - and the effects of lecanemab on this group of people needs further investigation.

[28] Inequalities in dementia: unveiling the current evidence and developing measures to quantify them. Besley et al, 2023, publication forthcoming.
[29] https://digital.nhs.uk/data-and-information/publications/statistical/primary-care-dementia-data
[30] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4678594/
[31] https://onlinelibrary.wiley.com/doi/abs/10.1002/ana.410170310?sid=nlm%3Apubmed

Other issues

13. Are there any other issues that you would like the committee to consider?	Lecanemab is the first disease-modifying treatment 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[32]; it allows optimal medical management to delay progression and rule out other possible causes of symptoms [33]; it can support risk reduction[34] and it is associated with reductions in care giver burden, fear and anxiety.[35] 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 lecanemab for unpaid carers as well as for people with dementia. As outlined earlier in our response, caring for someone with dementia 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 dementia needs to be considered. It will be important to be clear in communication on lecanemab 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.

[32] https://doi.org/10.3390/diagnostics6010006
[33] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2787842/
[34] https://doi.org/10.1002/14651858.CD006222.pub3
[35] 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.	○ **Dementia 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 dementia 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. ○ **Dementia 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 dementia 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.

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Single Technology Appraisal

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

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.

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. 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. 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.

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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 Alzheimer's disease and carers may see the main advantages of a disease modifying treatment, such as Lecanemab, 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, Lecanemab 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 Lecanemab 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.

Disadvantages of the technology

10. What do patients or carers think are the disadvantages of the technology?	A likely key disadvantage to Lecanemab 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 Lecanemab 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, the route of administration could be a disadvantage, as an intravenous administration every two 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 two weeks will require additional planning and organisation, for the person with Alzheimer's disease and/or their carers. This might be also 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 caregivers, 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. 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 Lecanemab can be effective.

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 Lecanemab. Those who are living independently with a timely diagnosis might well benefit the most, as receiving Lecanemab 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 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 Lecanemab, 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 Lecanemab 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 Lecanemab.

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 Lecanemab 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 Lecanemab 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 Lecanemab 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. 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 Lecanemab is to be administered intravenously every two 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 Lecanemab 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 Lecanemab 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 Lecanemab. Indeed, broader post diagnostic support must remain a priority, as Lencanemab 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 Lecanemab requiring additional financing and resources. Dementia UK also urges that patient and carer perceptions and experiences of the Lecanemab treatment and effectiveness be gathered and considered when assessing the clinical benefit of Lecanemab. 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 caregiver burden, 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 Lecanemab 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 Lecanemab 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.	• Lecanemab 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 Lecanemab can be achieved should therefore be carefully considered. • Communication around who is eligible for Lecanemab 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 Lecanemab, non-pharmacological post-diagnostic support must be integrated, and remain a priority, within clinical pathways.

Thank you for your time.

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[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

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

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.

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- Your response should not be longer than 13 pages.

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** A specialist in the treatment of people with this condition? **Yes** 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 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
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 Alzheimer's disease (AD) due to mild cognitive impairment (MCI) – to prevent or significantly delay progression to dementia over time • e.g. operationalised as Clinical Dementia Rating (CDR) change from 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, for example slowing of decline of about 30% in functional or quality of life measures would likely be a useful benefit for individuals • This might be represented by a change in a biomarker (e.g. amyloid load) **if** that was 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 – this is symptomatic treatment not disease modifying • Beyond that, 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 poorly defined and standards of care variably adhered to. The pathway is made more complex as there is fragmented service across multiple specialties with poor integration. Care varies enormously with some specialist centres providing molecular diagnostics, multidisciplinary diagnositc and support services, and others providing a very limited service due to insufficient resource. • No guidance for primary care diagnosis of dementia • Inconsistent pathway for referral from primary care to secondary/tertiary 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 causing significant workforce challenges. • 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, therefore the current diagnosis of Alzheimer's disease may not be accurate reflection of brain pathology • MRI/CSF recommendations as per NICE guidance are in place in some but not all centres • Amyloid PET is available in very few centres, and there is 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 of diagnostic tests 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. Patient selection to maximally benefit from the treatments would be key

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 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 Lecanemab is clearance of Aβ 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 phase 3 study (https://www.nejm.org/doi/full/10.1056/NEJMoa2212948) showed that treated patients had significantly attenuated rates of cognitive decline over 18m both in the primary outcome (CDR-SB) 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 we already consider the demonstrated benefits clinically meaningful. • If trial evidence is confirmed over longer-term follow-up (e.g. in a large prospective long-term follow-up Phase 4 post-marketing study), there is reason to expect potentially significant meaningful

	benefits in cognition and health-related quality of life including maintaining individuals' independence, decreasing carer burden and delaying time to institutionalisation.
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 β-amyloid – are most likely to benefit. • It is less likely that individuals with more advanced dementia will benefit. • The clinical trials suggest that there may be differences in response and side-effects in individuals with ApoE4 genetic variation, 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	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

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.)	and delivery of drug; monitoring for side-effects, efficacy and termination of treatment; and management of patient and societal expectation. 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, or progression of dementia without clear ongoing benefit
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 reduce 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

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 condition and the patient's quality of life?	MRI brain changes (Amyloid Related Imaging Abnormalities, ARIA) were seen in 17.3% (ARIA-H: haemorrhage) and 12.6% (AIRA-E: oedema) of individuals in the clinicals trial on MRI. The majority of these were asymptomatic. 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.

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 will receive the diagnostic work-up mandated by clinical trial protocols despite many aspects being recommended in NICE guidance.
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?	Lecanemab has demonstrated significant attenuation of cognitive decline, as well as clear evidence for disease modification (amyloid removal). Initially given accelerated approval on the basis of amyloid clearance, on July 6th the FDA Lecanemab a full licence on the basis that a clinical benefit had been proven in a confirmatory clinical trial. A licensing decision by the MHRA is awaited.
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) since the publication of NICE technology appraisal guidance TA217?	No
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.	• Lecanemab represents a new class of treatment for AD with evidence for disease modification, i.e. altering the natural course of the disease. • The evidence available to date shows that the drug has fundamental effects on core features of Alzheimer's disease (removal of amyloid plaques) and significant impacts on a range of cognitive outcomes. The major benefits are likely to be long term in terms of delayed conversion from MCI to dementia; and from independency to dependency and admission for institutional care. • 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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- Your response should not be longer than 13 pages.

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? Yes A specialist in the treatment of people with this condition? No A specialist in the clinical evidence base for this condition or technology? No Other (please specify):
5a. Brief description of the organisation (including who funds it).	The Faculty of Public Health (FPH) is a registered charity and a joint faculty of the three Royal Colleges of Physicians of the United Kingdom (London, Edinburgh and Glasgow), with around 5,000 members. Its aims are to promote for the public benefit the advancement of knowledge in the field of public health; to develop public health with a view to maintaining the highest possible standards of professional competence and practice; and to act as an authoritative body for the purpose of consultation and advocacy in matters of educational or public interest concerning public health. It is a professional membership association and is primarily funded by membership subscriptions.
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.)	Lecanemab, 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 would 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, 2.32 for MMSE, and also 3 for ADAS-Cog11. 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, is in 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 lecanemab 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 pathology on PET scan or CSF, 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% would meet the lecanemab trial eligibility criteria (*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, and even less of the total population with dementia, e.g. including those presenting through old age medial settings, would meet eligibility criteria. Despite the low eligibility, many would seek treatment, and 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 vast 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). Scrutiny of those who managed to persist until the end of the lecanemab trials would be important (the trials included only highly selected volunteers who were motivated to join a clearly intensive intervention). 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 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 deemed necessary prior to consenting for treatment, the resource implications may need to include genetic counselling, itself problematic and not routinely considered at present. For those determined to be eligible, a new treatment pathway would need to be created that funded and facilitated fortnightly infusions 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. Though not reported directly for the lecanemab phase III trial, in the recent donanemab trial, 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. The lecanemab trial did not include treatment completion as part of the trial procedures, so treatment would either need to continue indefinitely (with associated implications), or more likely, an approach similar to that of the donanemab trial would need to be explored in which serial amyloid measurements are used to inform cessation of treatment. Presumably, patients would then 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. 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 atrophy 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 lecanemab were approved for only a small group that closely resemble the trial population (circa 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 fortnightly infusions at specialist centres for a possibly indefinite period 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 used? (For example, primary or secondary care, specialist clinics.)	It is likely that lecanemab 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 patients and their carers, who would need to be able to attend these specialist centres every fortnight. These would not necessarily be close to where they live. The healthcare personnel required for the diagnostics, fortnightly 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, 2.32 for MMSE, and also 3 for ADAS-Cog11. The phase III trial of lecanemab (60% MCI, 40% mild AD) reported effects of 0.45 for CDR-SB, and 1.44 for ADAS-Cog11, relative to placebo. Thus, after 18 months of treatment with lecanemab, the treatment effects represented less than half of what is considered clinically meaningful. The lecanemab treatment effect of 0.45 is smaller than the smallest increment on the CDR-SB scale (0.5), the primary trial outcome measure. Moreover, 'functional unblinding' due to common infusion reactions (26.4% of patients in treatment group compared to 7.4% in placebo group), and higher drop-out in the intervention arm (84.4% of placebo group completed treatment vs. 81.2% of lecanemab 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 about half of the effect of the only currently available drugs, cholinesterase inhibitors/memantine after 6 months of treatment. And even these drugs have 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 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., 2023. The debate around the new Alzheimer's drugs has overlooked a vital limitation: the population mismatch'*. The recruitment centres for the lecanemab trial took 2 years to recruit an average of 9 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 only half of 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 almost 1 in 5 patients on lecanemab did not complete the phase III trials, 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 and have longer life expectancies.
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. Although not published in the main trial report, health-related quality of life outcomes have been published in a follow-up publication (*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.

	There are four reasons why it is not possible to infer with confidence whether these statistically significant differences will translate into meaningful improvements in quality of life beyond current care. (1) As with all outcomes for lecanemab, 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 lecanemab trial recruited only 9 patients each during a 2 year 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 trial populations (*Burke et al., 2023. Lecanemab - Looking Before We Leap. Neurology*). Subgroup analyses from the phase III trial 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 themselves confirmed that the 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).

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.)	Lecanemab would be much more difficult than existing treatments. Lecanemab 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 (70% in the phase III trial, 92% 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 fortnight for an 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. Fortnightly 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 include any additional testing?	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. The phase III trial of lecanemab did not include a set process for cessation of treatment. As described above, it may be possible (though without direct trial evidence to support this) to adopt treatment cessation processes similar to that of the recent donanemab trial. In this trial, serial PET scans were undertaken to determine when brain amyloid levels dropped below a set threshold, at which point treatment was stopped. There would then,

	presumably (again 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 lecanemab. 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 management of the condition?	Given the answer to q16 above, and within the confines of current evidence, no.

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?	Yes. The phase III trial showed that, in keeping with other drugs in this class, lecanemab causes significant adverse events. 12.6% (113/898) of participants treated with lecanemab developed brain oedema detectable by imaging (placebo group 1.7%), 22% of whom were symptomatic. 17.3% (placebo 9%) experienced brain haemorrhage, almost always asymptomatic, though the long term effects are unknown. 6.9% (placebo 2.9%) experienced adverse events severe enough to discontinue the trial. Numbers of deaths in both groups were comparable during the main trial (lecanemab 6/898, placebo 7/897), but during the trial's open label extension there have been deaths due to brain haemorrhage associated with taking lecanemab 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 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 that is 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 ending treatment and subsequent monitoring of re-accumulation of amyloid pathology 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, the number of deaths were small (<10 in each arm), and there was no discernible difference between the treatment group and the placebo control. However, in the open label extension of the drug, 3 deaths were

not apparent in clinical trials but have come to light subsequently?	reported to be associated with lecanemab use alongside therapies which inhibit blood clotting (i.e. anticoagulants and thrombolysis) https://www.science.org/content/article/clinical-trial-participants-autopsy-brain-exam-stoke-alzheimers-drug-fears. It is important to note that these are news reports and therefore low-quality evidence. However, given the high-rate of brain haemorrhage in the treatment arm of the trials, the notion that lecanemab with concomitant use of anticoagulants or thrombolysis would increase the risk of fatal bleeding is biologically plausible. Moreover, the lecanemab 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 lecanemab 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., 2023. The debate around the new Alzheimer's drugs has overlooked a vital limitation: the population mismatch* 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 Alzheimer's disease' in the phase III trial of lecanemab, 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 lecanemab. Further, population evidence shows that the 'pure' Alzheimer's seen in the trial cohorts (i.e. amyloid 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 evidence from '*Walsh et al., 2023. The debate around the new Alzheimer's drugs has overlooked a vital limitation: the population mismatch'* 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 9 participants each over a 2 year recruitment period, and the trial exclusion rate was 70% (i.e. for every 10 people tested for eligibility, 7 were deemed ineligible – the effect this rejection has on patients and their caregivers is an externality of any analyses of lecanemab 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 lecanemab's case, the hypothetical pathway would tick each of these boxes, primarily driven by the need to attend infusion centres fortnightly, 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 lecanemab's approval.

Key messages

23. In up to 5 bullet points, please summarise the key messages of your submission.	• Evidence does not support that lecanemab 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 short duration. • 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. 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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Single Technology Appraisal

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

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.

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2. Name of organisation	Faculty of Old Age Psychiatry, Royal College of Psychiatrists
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): 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 example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	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-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: • 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 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 about 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). 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 measures 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) 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 emphasises 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, many of existing rating scales have limitations 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) – so more recent clinical trials have developed different rating scales to try and address this (for example for lecanemab - ADCS-MCI- ADL and the ADCOMS). 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).

Clinical Trial Outcomes	Measures	Emerging / Novel Measures
Conventional outcome measures - Cognition - Function - Behavioural - Neuropsychiatric - Global **Patient-reported outcomes (PROs)** - minimal important difference (MID) **Care partner reported outcomes** - quality life / stress - burden **Socioeconomic variables** - resource utilization	**Effect size (Cohen's D, SRM)** **Risk ratio / odds ratio** **Numbers need to treat** **Numbers need to harm** **Time to event** **Meaningful change and difference** thresholds – minimal clinical meaningful difference (MCID)	**Cumulative benefit:** Increasing drug-placebo difference over time **Predictive benefit:** Biomarker-based prediction of outcome **Progression time saved/gained**

c) A further factor we think is relevant in answering this question relates to extent of clinical change observed in the placebo group in the lecanemab 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 primary outcome measure – Clinical Dementia Rating Sum of Boxes (CDR-SB) – the placebo group declined by 1.66 points on this 18 point scale over 18 months (compared to 1.22 in the lecanemab group).

d) Finally – it is important to note that cholinesterase inhibitors are prescribed for the dementia stages of AD – so for the lecanemab study approximately 38% subjects were diagnosed with mild AD (so had threshold to a dementia diagnosis) and indeed just over 50% were also receiving approved treatments for AD. A further debate in the literature has centred on how the effect size seen in clinical trials with DMTs like lecanemab compares to established treatments using CHEI and memantine. We are of the opinion that drawing direct comparisons is problematic because of differences in how the trials were designed – such different use of biomarkers, diagnostic and eligibility criteria, stage of illness, statistical approaches, trial duration, and rating scales – so whilst is it tempting to draw direct comparisons (for example metanalysis of 13 CHEIs studies of mild to moderate dementia showed an average MMSE difference of 1.37 points and ADAS-COG difference of 2.7 points (*Birks J, 2006, Cochrane database Syst Rev*) this can be problematic.

Taking these issues and findings into consideration – when answering this question we are of the opinion that clinically meaningful benefit would be supported by:

1. **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. It is our understanding that no clinical trial in AD (prior to lecanemab) has demonstrated this pattern of benefit in this patient population
2. **Focusing on CDR-SB as the primary outcome measure,** this composite measure clinically evaluates both cognition and function involving both the participant and their carer, and we are of the opinion that a difference in change of around 0.50 on this scale over 18 months represents a meaningful though modest clinical benefit.

	3. We also think converting the **difference in CDR-SB over time into a proxy measure for "time saved"** offers 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 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. 4. **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 lecanemab 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,	For patients with AD dementia (mild, moderate, and severe) there are recognised treatments (cholinesterase inhibitors and memantine) as approved by NICE (NG97 2018). Lecanemab has been approved in the USA by the FDA and therefore product licensing information exists outlining how this medication should be prescribed. In addition – 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,

and if so, which?	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 lecanemab is approved, it is our opinion these AUR criteria (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 way to balance the benefits vs risks of using lecanemab 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 lecanemab. [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 lecanemab 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 lecanemab could represent a clear shift in the way we think about and approach managing dementia as a whole. It could lead to a range of benefits, offering 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, estmates 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. 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.
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	We believe it would not be possible to offer lecanemab within existing services as "business as usual". We are of the opinion that access to lecanemab (and any other future approved monoclonal antibody) would be best overseen by diagnostic and treatment hubs, as suggrsted 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. 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. To prepare, auditing access to MRI, amyloid PET scanning and CSF sampling as well as establishing what pathways are currently in place for people with a diagnosis of mild cognitive impairment will help inform what additional practical steps are needed for services to adapt, locally and regionally, to deliver new treatments. Understanding the factors that impact on current delays in accessing a timely diagnosis will also be important. A network of hubs could also provide a platform for future research and link with the strategic initiatives across the dementia clinical-research ecosystem. There will, for example, be a need to better understand the needs of people who are amyloid positive yet ineligible for mAbs and how they are best supported: this may be more frequent than expected outside of research centres and likely to reflect the complexity of cognitive disorders.
10a. How does healthcare resource use differ between the technology and current care?	Reply is largely detailed in previous section.
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.
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 lecanemab with current practice is that for patients with MCI-AD there are no existing treatments. However – using the criteria we set out in section 7 we are of the opinion that: 1. 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. It is our understanding that lecanemab was the first clinical trial to demonstrate this pattern of benefit in this patient population (noting the outcome measures in the lecanemab trial also for the first time included measures of quality of life and carer burden). 2. Focusing on CDR-SB as the primary outcome measure, this composite measure clinically evaluates both cognition and function involving both the participant and their carer, and we are of the opinion that a difference in change of around 0.50 on this scale over 18 months represents a meaningful though modest clinical benefit. This was achieved. 3. We also think the conversion of this difference in CDR-SB between lecanemab and placebo groups into a proxy measure for "time saved" offers a novel and intuitive way of describing whether or not a drug is likely to be clinically beneficial – and we think in the a difference of around 4-6 months represents a clinically meaningful benefit that patients' would find helpful when considering whether (or not) this treatment is right for them. This was achieved. 4. Using global CDR scores – to slow the progression from one stage of AD to the next: participants on lecanemab had a 31% lower risk of converting to next stage of disease by global CDR c/w placebo. Individuals also remained in earlier stages of Alzheimer's disease for a longer period of time.
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 lecanemab 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?	If proven this could be a major advantage as AD is associated with significant detrimental personal, family, societal and health costs. Quality of life measures were statistically significant better in lecanemab c/w placebo.
12. Are there any groups of people for whom the technology would be more	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

or less effective (or appropriate) than the general population?	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)

The use of the technology

13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care?	Lecanemab 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 the AUR (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 there is little value to continuing. Evidence to support prescribing a time limited course of lecanemab comes from design of the phase III donanemab study where possible stopped treatment on becoming amyloid negative (mean time was 47 weeks over 18 months) and despite stopping treatment participants continued to show benefits c/w placebo at 18 months. 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 the quality-adjusted life year (QALY) calculation?	Possibly,
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 see merit in conducting further clinical trials so the long-term evidence of lecanemab can be determined more clearly. Biomarker positive results from PET, CSF and blood) relating to amyloid, tau, neurogranin (synaptic dysfunction) and glial fibrillary acidic protein (GFAP - marker of astrocyte activation)
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 lecanemab will be to optimise its safe use. ARIA and infusion reactions are clear adverse events that require careful consideration and monitoring. 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 emerging evidence of accelerated cerebral atrophy. Importantly, there is a need to better understand the risk of mortality: though no excess deaths were reported in the phase III study with lecanemab, three fatalities have been reported in the open label extension which the site principal investigators attributed to lecanemab.

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 lecanemab together point to a clear dose and time response to the clearance of amyloid as measured by both PET-amyloid and CSF biomarkers – and importantly changes were also seen in other key pathological pathways involving tau, neurogranin and GFAP. This is consistent with changes in amyloid also having a downstream impact of other pathological events that in turn could convey clinical benefits.
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: though no excess deaths were reported in the phase III study with lecanemab, three fatalities have been reported in the open label extension which the site principal investigators attributed to lecanemab. (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 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?	No - though similar results to the lecanemab trial has not been observed in the donanemab phase III trial: 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).
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 lecanemab (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. Lecanemab is a monoclonal antibody treatment, and more DMTs may follow. 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 lecanemab 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. Clinical benefits with lecanemab were observed across all primary and secondary outcome measures as well as changes in core pathological targets relating to amyloid, tau, neurogranin and glial fibrillary acidic protein. This profile of clinical and biological changes is first in kind in the treatment of Alzheimer's disease. 2. There are important safety concerns that must be considered with clear risk mitigation strategies. 3. Delivering lecanemab 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 lecanemab. 4. To tailor and guide decisions about the eligibility for treatment, we support 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 lecanemab 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 lecanemab (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

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

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.

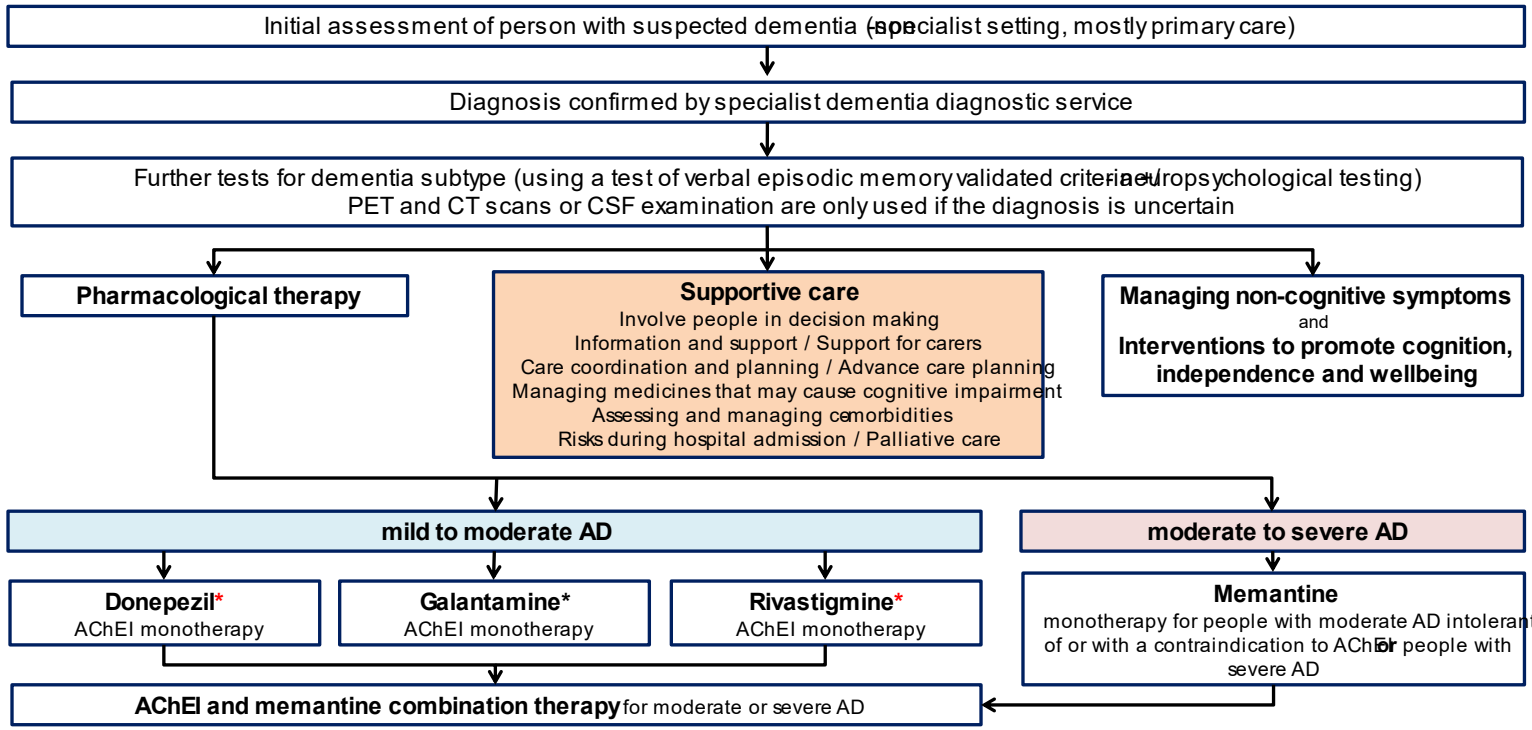
About you

1. Your name	Ann Jarvis
2. Name of organisation	NHS England
3. Job title or position	Programme Director (Clinical Strategy)

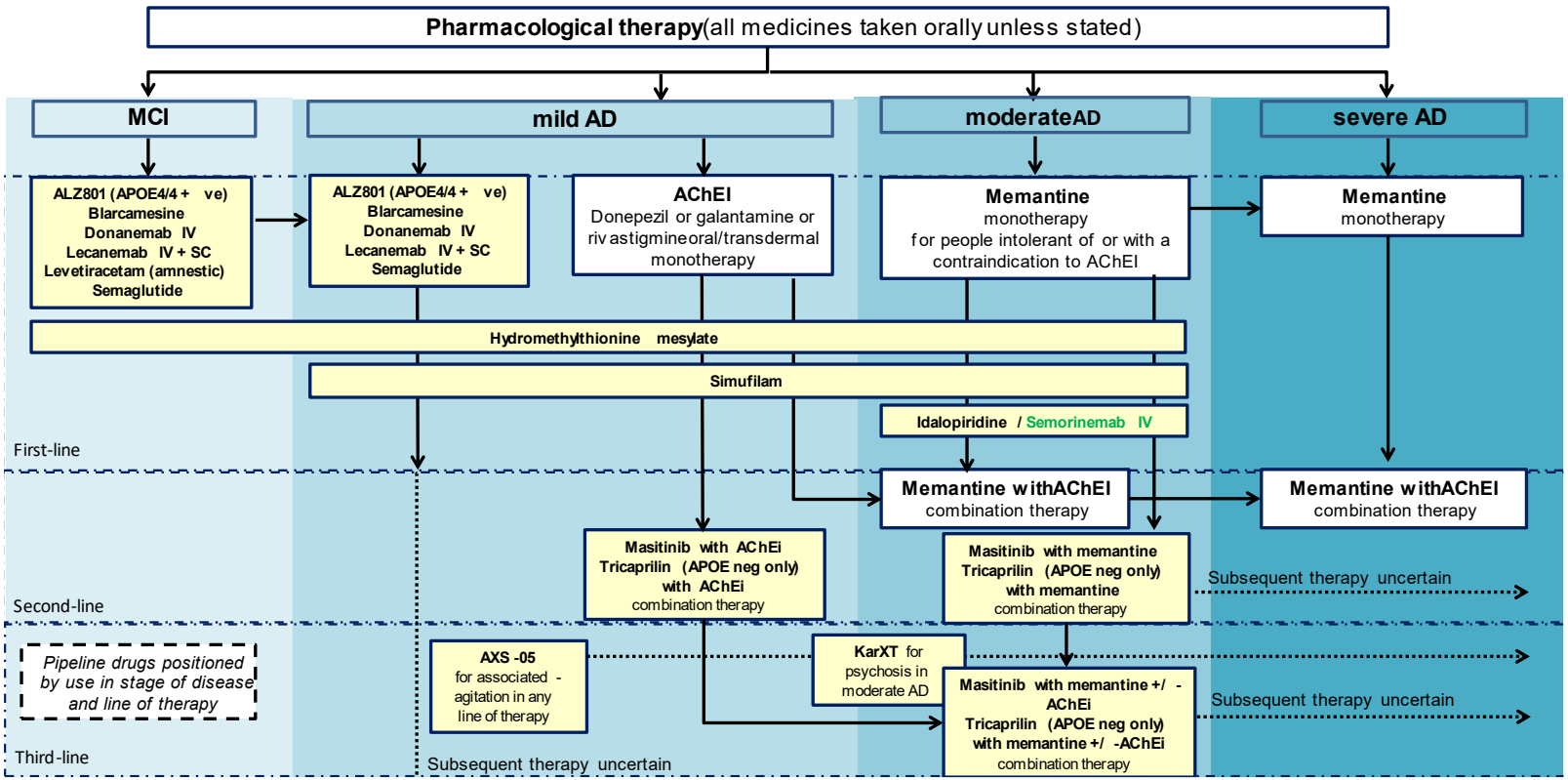
4. Are you (please select Yes or No):	Commissioning services for an ICB or NHS England in general? Yes or No Commissioning services for an ICB or NHS England for the condition for which NICE is considering this technology? Yes or No (PET-CT and APOE-4 Genetic Testing) Responsible for quality of service 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 the use of digital technology, research and innovation, and to deliver 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. 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

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 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** 

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 receive marketing authorisation and subsequently be recommended as clinically and cost-effective by NICE. Products such as lecanemab are being initially developed for mild cognitive impairment (MCI) and mild dementia due to AD, which will result in patients with earlier / milder forms of Alzheimer's being eligible for potential treatment with disease modifying therapies (DMTs). There are a number of key changes to the current pathway which would result from the availability of products such as lecanemab, 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 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 • 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 in monitoring for amyloid clearance during treatment. • Increase in MRI capacity • New requirement for amyloid radiotracer supply • Expansion of genetic testing (with a new standalone APOE04 test requirement) and counselling services • Increases in demand on secondary care infusion services and additional IV capacity requirements • Increases in demand on secondary care services in the management of ARIA



The use of the technology

9. To what extent and in which population(s) is the technology being	Lecanemab is not currently being utilised within 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 – lecanemab would require a pathway redesign to accommodate the product.
10a. How does healthcare resource use differ between the technology and current care?	Please see section 8 above for further details – lecanemab would be associated with significant additional resource requirements should NICE recommend the technology as a clinically and cost-effective use of NHS resources.
10b. In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	As a new medicine, lecanemab 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. Lecanemab will need investment in services and staff to allow delivery of bi-monthly IV infusions and monitoring for (and management of) ARIA-E. Presence of amyloid beta pathology must be confirmed before starting treatment. In the US and Japanese licenses, a test for ApoE ε4 status to inform risk of developing ARIA is recommended (a stand alone test for ApoE ε4 in dementia is not currently listed in National Genomic Test Directory). Lecanemab may be suitable for homecare particularly s.c. formulation, which may not be available initially (i.v. depends on formulation/product stability). GPs will need upskilling in early patient identification; and community assessment and diagnostic pathways needed to identify amyloid-positive MCI.
10d. If there are any rules (informal or	After initial specialist assessment (which includes neurological examination and cognitive testing), dementia subtype may be diagnosed using a test of verbal episodic memory, validated criteria +/- neuropsychological

formal) for starting and stopping treatment with the technology, does this include any additional testing?	testing. PET and CT scans or CSF examination are only currently used by exception if the diagnosis is uncertain and this would need to be expanded for lecanemab. A test for ApoE ε4 in dementia is not currently listed in the National Genomic Test Directory. In the lecanemab PII trial, ~70% were APOE ε4 carriers. The current long-term clinical data associated with lecanemab (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 treatment with lecanemab. 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 primary care practice, memory clinics and infusion capacity is likely to impact the number of patients treated.
12b. Consider whether these issues are different from issues with current care and why.	Lecanemab is the first 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.

Thank you for your time.

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NICE National Institute for Health and Care Excellence

Single Technology Appraisal

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

Clinical expert statement

Information on completing this form

In part 1 we are asking for your views on this technology. The text boxes will expand as you type.

In part 2 we are asking you to provide 5 summary sentences on the main points contained in this document.

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. Please type information directly into the form.

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.

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 **Friday 29 March 2024**. 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.

Part 1: Treating mild cognitive impairment or mild dementia caused by 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	Richard Perry
2. Name of organisation	Imperial College Healthcare NHS Trust
3. Job title or position	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 mild cognitive impairment or mild dementia caused by Alzheimer's disease? ☒ A specialist in the clinical evidence base for mild cognitive impairment or mild dementia caused by 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.) I don't know if they submitted one – I have had no communication to that effect
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 mild cognitive impairment or mild dementia caused by Alzheimer's disease? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	To slow down progression of a progressive neurodegenerative disease and allow patients to retain independence for longer, thereby improving quality of life and decreasing burden on carers and health and social care
9. 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)	Delay of progression from MCI to dementia by 4-6 months would be clinically significant
10. In your view, is there an unmet need for patients and healthcare professionals in mild cognitive impairment or mild dementia caused by Alzheimer's disease?	Yes, there is a very large unmet need for both patient and healthcare professionals. For patients, there are no licensed treatments that have demonstrated efficacy in slowing down the progression for the condition. For HCPs there are no NICE guidelines for MCI, and expertise in, and use of, biomarkers for accurate early diagnosis of Alzheimer's disease in the UK are poor and lag behind the rest of Europe
11. How is mild cognitive impairment or mild dementia caused by 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?	NICE guidelines for dementia but no guidelines for MCI MCI is currently poorly managed in the NHS with lack of public health messaging, lack of training and support for primary care, secondary care often not diagnosing or giving misleading information, lack of coding, and lack of understanding, provision, and use of diagnostics including CSF and amyloid PET. There is variability across England, but the variability is mostly between poor and very poor, and the islands of good practice are small and not well supported by current commissioning models. The technology would have a major impact on the pathway of care for MCI due to AD in terms of better public understanding, enabling improved equity of access for under-represented groups in diverse populations, improved primary care education and recognition and more accurate diagnosis to provide patients with the appropriate clarity of diagnosis as a platform for effective management. With stroke care, a minority of people were eligible for thrombolysis and

	thrombectomy, but with the introduction of these therapies and central organisation of improved services to deliver them, the overall care, and death and disability, of stroke patients improved considerably, even if they weren't thrombolysed. The technology would help bring the pathway of care into the 21st century and help the UK to start to catch up with our colleagues in Europe.
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)	No, the technology would be a sea change in NHS practice. 1. Likely increase in demand on primary care as awareness of MCI and DMT increases a. Upskilling of GPs needed including apps and other tools b. Role of nurse practitioners and PAs c. Requirement for referral guidelines – these should be national and not locally determined as this will lead to inequalities of care and variable quality services d. Public health messaging 2. Increased use of MRI. Requirement of training for radiologists to detect ARIA 3. Diagnostics in form of lumbar punctures and amyloid PET a. Specialist training required ? nurses, PAs, governance, supervision b. Provision of lab services and quality control checking 4. Infusion capacity. 50 patients means 5 patients per day. Need RGNs, infusion suites etc 5. ApoE testing. Probably best with private provider. Do not need specific genetic counselling – can be done by treating team as in other countries 6. Management of side effects (predominantly ARIA but also infusion reactions)

	The technology should initially be used in a secondary / tertiary care setting as per published Appropriate Use Recommendations (Cummings et al), by a team with experience of using similar drugs, that incorporates experience of using and interpreting the diagnostics (CSF and PET), discussing drug treatment and brain related side effects with patients, giving biological drugs via infusion, and monitoring for side effects. Those in other secondary care sites, such as local memory clinics, should initially work with a specialist centre or hub, to disseminate learning and set up their own services with links in via MDT to improve governance, safety, and learning, so that borough based services can develop safely. If psychiatrists are to be delivering the medication, they will need support and training from neurology in diagnostics, delivery and monitoring as these drugs are not dissimilar to other drugs use in neurological disease (e.g. MS and myasthenia)
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?	Yes, the evidence suggests that the treatment will provide clinically meaningful benefits to selected patient group. There is insufficient data to make conclusions about length of life but there is data to support improved activities of daily living and quality of life over those not on treatment
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	More effective earlier in disease course. Evidence from multiple studies points to increased effectiveness earlier in course of disease – i.e MCI due to AD group
15. Will the technology be easier or more difficult to use for patients or healthcare professionals than	Yes, much more difficult – see number 12 for a detailed answer.

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)	
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Yes, see above in number 12. Appropriate Use Recommendations exist in USA and will be published in UK also. Stopping treatment will be dependent on licensing parameters and guidelines but likely to be after a 18 month course of treatment as per the Phase 3 clinical trials
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	The missing data is the longer term benefit after 18 months of treatment. The data to 18 months suggests 4-6 months delay in disease progression. The treatment group and placebo trajectory continues to diverge at 18 months, in line with disease modifying effect (seen in both lecanemab and donanemab). It is likely that 3 years after initiation of treatment with an 18 month course of lecanemab, the delayed progression will be longer than 4-6 months and probably around 8-12 months. This can be seen on extrapolation of the data but unlikely to be provided by the clinical trials as it is not viable to run placebo groups for 3 years. Please see use of ADNI data to form comparison group – presented by R Sperling, MGH/Harvard at CTAD conference, Boston, Oct 23.
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?	The technology is innovative and its introduction will lead to significant and substantial impact and health benefits for those who receive the treatment and also for all those in an aging population who will benefit from increased public and primary care awareness of brain health whether it be by screening and pharmacological intervention of by enhanced lifestyle interventions to reduce dementia rates. In other words, although the technology is likely to be administered to a small proportion of patients with AD, its introduction will catalyse significant improvements in healthcare with respect to prevention, recognition, management, and care of Alzheimer's disease and other dementias across the spectrum.

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 side effects need to be managed, like any other medication. In this situation, there is significant concern amongst psychiatrists who are not experienced or skilled in managing brain related side effects of biological therapies and who will need to acquire skills through interdisciplinary working. As a neurologist with ten years' experience of administering drugs like this, I am comfortable with the side effect profile and the management of the side effects. The side effects are manageable by appropriately trained and experienced physicians as ARIA rates are low (ca 15%) and mostly asymptomatic. Symptomatic ARIA is only 3% and macrohaemorhage rates (which are the most significant concern to clinicians) are approx. 0.3%.
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 key differences in the clinical trials from current UK clinical practice are: 1. Trial participants were selected on basis of amyloid positivity. UK practice lags behind Europe and US on use of biomarkers to determine amyloid positivity and this difference reflects on the state of UK practice rather than the trials 2. The clinical trial population was younger than most memory assessment service populations 3. The clinical trial population was less ethnically diverse than the UK population The most important outcomes are defined by the FDA and require positive outcomes on measures of both cognition and activities of daily living. The primary outcome measures are those that have been used in clinical trials of Alzheimer's disease for many years and are considered standard in the field. They main outcome measures are better suited to patients in the dementia phase of the illness rather than in the MCI phase where the outcome measures are not designed to pick up much smaller and slower rates of change. Unfortunately the choice of outcome measures are limited by the FDA but those used are standard and accepted in this field.

	There has subsequently been a lot of discussion on the difference between a statistically significant trial outcome and a clinically meaningful trial outcome. As a clinician, my experience tells me that what patients want is 'time', as in, they would like a treatment to enable them to maintain independence and their activities for longer. Delay to progression was not a nominated primary outcome measure as this is moderated by the FDA, and subsequent calculations have provided analysis of the delay in progression, say from MCI to mild dementia. The delay seems to be about 4-6 months after 18 months of treatment. This seems a mild effect but the extrapolated data, or comparison to ADNI data sets (see Sperling et al CTAD, Boston Oct 23) suggest more benefit over longer periods of time, after treatment has stopped. This is very difficult to demonstrate in a clinical trial as it would mean keeping people on a placebo arm for 3 years or more. The outcome measures used on the trial do not accurately predict longer term outcome, with the currently available data. This is primarily a result of the technology being new and longer term outcome data will accrue with time. In terms of possible adverse effects that have subsequently come to light, there are probably two that have raised discussion: 1. Use of anticoagulants. Patients on the trial could use anticoagulants such as DOACs. These may increase risk of bleeding and change the probability of side effects such as macrohaemorrhage – the key potential side effect to avoid. Since publication of the trial data, Appropriate Use Recommendations have suggested that lecanamab should not be given to those on anticoagulants, a decision that is likely to reduce risk of brain bleeds and improve the overall safety profile. 2. Patients of amyloid targeted monoclonal antibodies have been shown to lose brain volume on MRI scans. This is not a new finding and was reported in trials of bapineuzumab over ten years ago. The mechanism is unclear but has been postulated to result from decreased inflammation or removal of amyloid. Given that the patients did better, despite this finding,

	it remains an unexplained outcome that requires further explanation but should not be a cause of undue concern
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	Outcome data has been modelled using matched ADNI datasets and demonstrates improved QALY outcomes for longer term treatment (Igarashi et al 2023).
22. Are you aware of any new evidence for the comparator treatments since the publication of NICE technology appraisal guidance TA217?	No
23. How do data on real-world experience compare with the trial data?	I do not know of any relevant data that is available.
24. 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	I do not anticipate an equality issues with administration of treatment with lecanemab. I am concerned that people from particular ethnic backgrounds may be disadvantaged in being seen and evaluated for treatment with this drug, but this concern reflects the wider concerns about access to multiple medical treatments for people whose language, education and culture form a barrier to accessing healthcare. While this problem is not specific to this treatment, addressing the problem with respect to this treatment is important and places emphasis on optimising the public health messaging. There have been concerns raised about people with Down's Syndrome and their access to treatment, primarily because the rates of AD pathology and amyloid positivity are so high in this group. This group were not part of the clinical trial evidence on which a license is likely to be issued, and would not be excluded form treatment on the basis of disability, but on trial evidence and licensing.

• 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.	

Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

Lecanemab treatment can slow down progression of a progressive neurodegenerative disease and allow patients to retain independence for longer, thereby improving quality of life and decreasing burden on carers and health and social care

The technology is innovative and its introduction will lead to significant and substantial impact and health benefits for those who receive the treatment and also for all those in an aging population who will benefit from increased public and primary care awareness of brain health whether it be by screening and pharmacological intervention, or by enhanced lifestyle interventions to reduce dementia rates

The side effects are manageable by appropriately trained and experienced physicians as ARIA rates are low (ca 15%) and mostly asymptomatic. Symptomatic ARIA is only 3% and macrohaemorhage rates (which are the most significant concern to clinicians) are approx. 0.3%.

The technology would require a sea change in NHS management of Alzheimer's disease with greater emphasis on early and accurate diagnosis, use of biomarkers to bring UK into line with other European countries, and liaison between physicians and psychiatrists to develop a skilled workforce to manage biological drug administration and monitor and manage side effects.

This technology is the start of an era of earlier recognition and diagnosis of a common neurodegenerative disease that will advance with multiple therapeutic options for prevention and treatment in the next ten years. Adoption of this technology would provide numerous challenges but if these challenges are not met and overcome now, they will have to be overcome later, and meanwhile UK patients with the early stages of Alzheimer's disease will continue to receive care that is not of an acceptable standard

Thank you for your time.

NICE National Institute for Health and Care Excellence

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NICE National Institute for Health and Care Excellence

Single Technology Appraisal

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

Clinical expert statement

Information on completing this form

In part 1 we are asking for your views on this technology. The text boxes will expand as you type.

In part 2 we are asking you to provide 5 summary sentences on the main points contained in this document.

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. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

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 **Friday 29 March 2024**. 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.

Part 1: Treating mild cognitive impairment or mild dementia caused by 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	Professor Elizabeth Coulthard
2. Name of organisation	University of Bristol
3. Job title or position	Professor of Cognitive Neurology
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 mild cognitive impairment or mild dementia caused by Alzheimer's disease? ☐ A specialist in the clinical evidence base for mild cognitive impairment or mild dementia caused by 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 mild cognitive impairment or mild dementia caused by Alzheimer's disease? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	To stop disease progression such that people retain functional ability and quality of life. Lecanemab would be the first therapy to slow disease progression if approved.
9. 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)	1) In those with Mild Cognitive Impairment (MCI) - prevention or delay of progression from MCI to dementia. Extensive conversations with our MCI patients suggest that 4-6 months delay of disease over 18 months is clinically meaningful to them. 2) In those with dementia – slowing of disease progression to enable prolonged good quality life. The minimum important slowing would be around 6 months over 18 months for the mild dementia patients with whom I have had spoken. 3) In both MCI and dementia, slowing of cognitive decline [such that people retain cognitive skills and, therefore, capacity to engage with and enjoy day-to-day activities].
10. In your view, is there an unmet need for patients and healthcare professionals in mild cognitive impairment or mild dementia caused by Alzheimer's disease?	Yes. We have very limited therapeutic options. Currently these are limited to symptomatic therapies for dementia only (not MCI) that at best enhance cognitive function by 2 or 3 points on a 30 point scale, and have significant side effects. There are no current disease-modifying therapies for Alzheimer's at any stage.
11. How is mild cognitive impairment or mild dementia caused by 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.)	NICE guidelines for dementia [NG97] – not specific to Alzheimer's disease. There are no NICE guidelines for MCI or presymptomatic Alzheimer's disease. Care pathways vary regionally and across disciplines, for example, while most regions have old-age psychiatry led memory services, some regions have primary care-led diagnosis with memory clinics being involved only in more diagnostically challenging cases. Alongside these memory services, some larger centres have neurology-led services where biomarkers are used for precise Alzheimer's diagnosis. Around 1% of people with cognitive symptoms have currently have precise diagnostic testing with biomarkers (CSF/PET).

• What impact would the technology have on the current pathway of care?	Essentially, in the absence of treatments, services have prioritised post-diagnostic dementia community support and symptomatic care rather than early, accurate diagnosis. Lecanemab would require biomarker diagnosis and therefore augmentation of the biomarker-led diagnostic pathway. Even without disease-modifying therapies, our patients now often ask for an accurate diagnosis to explain their symptoms even at an early stage. Patients tell us that this sometimes alleviates their anxiety as they understand the problem and allows them to plan their lives. It also allows better defined care. Given the intrinsic value of early accurate diagnosis, the improved diagnostic pathways that would be required to deliver lecanemab would have a positive impact on wellbeing in themselves.
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)	Lecanemab would be used in a largely different (although overlapping) population to that receiving current NHS dementia care. Current dementia diagnosis is late; referral from a GP requires people to be significantly cognitively impairment (e.g. not be able to draw a clockface or remember 3 words). Lecanemab was shown to work at MCI or early dementia stages of Alzheimer's. Some people are being diagnosed at early stages now, but many are not. Lecanemab would be best given in the specialist setting until we have more clinical experience of the drug and side effect management. We envisage data collection as part of routine care as the drug is introduced – that way we will build knowledge about where the drug is best given and by whom. Currently, most people who present with memory symptoms and are referred for further investigation by the GP attend memory services. In these services, patients have a clinical review, cognitive testing and, usually, a CT head. This allows for ~70% diagnostic accuracy for Alzheimer's which has been accepted in routine clinical practice. To receive lecanemab, patients would need to have

	molecular evidence of Alzheimer's disease giving a much higher diagnostic accuracy for Alzheimer's disease. Therefore clinics require access to biomarker testing (cerebrospinal fluid obtained through lumbar puncture or amyloid PET scanning) to deliver lecanemab. Currently, clinical management of Alzheimer's disease is focussed on cognitive enhancer medications (of very modest benefit in around half the people who receive them) and community support. To deliver lecanemab, clinics would need access to MRI (to detect the commonest side effects – Amyloid Related Imaging Abnormalities (ARIA)), an infusion suite/room, trained nurses, pharmacy staff, and acute hospital for management of side effects, plus possibly to test Apoe4 genetics (to stratify side effect risk). Note that ApoE genetics testing is not currently recommended by NICE and almost no NHS services do this test. Blood biomarkers are probably on the brink of being clinically validated as useful tools at least for triage of people with possible Alzheimer's. These would make diagnosis much more efficient.
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?	I expect the technology to improve health-related quality of life compared to current care. Current care is symptomatic only and the cognitive enhancers are of very limited benefit that is limited by side effects.
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Subgroup analyses for lecanemab clinical trial were generally underpowered, but there was a fairly convincing trend towards apoe4 predicting clinical response to lecanemab (apoe4 non-carriers having best clinical outcomes with apoe4 homozygotes having a poorer clinical outcome – possibly due to ARIA). Long-term data collection as part of clinical delivery of lecanemab is critical to understand sex, ethnicity and other sources of variation in the clinical benefit of lecanemab.

	Clinically, I see patients who are younger (~<75 years) and otherwise fit who would particularly appreciate the opportunity to receive lecanemab as they perceive the potential for even a few months prolonged independence as very positive. Some are trying to maintain jobs or independent living and the value of treatment to them appears more striking than for people who may already be frail for other reasons.
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)	The treatment would need a separate pathway from current care. At every stage of the delivery pathways that have been proposed, there are implications for patients and clinical staff, for example, 1) Presentation to GP – more people are likely to present to their GP with mild cognitive symptoms and an efficient triage system will be required. 2) Diagnosis - treatment would require early diagnosis with biomarkers which is currently only performed in specialist centres and reaches ~1% of patients who present to memory clinics. 3) Neuroimaging - Instead of a single CT, repeated MRIs will be required – possibly stressing local MRI capacity. 4) Delivery of drug – will require expert pharmacy, general nurses and infusion suites- none of which are part of current care. 5) Management of side effects will need medically trained teams in acute hospitals and more MRI resources. 6) Predicting side effects may well require ApoE genetic testing that is not currently performed. Overall lecanemab delivery would be much more involved than current diagnostic and treatment practices for people with early disease. Current treatments for early Alzheimer's dementia (donepezil/galantamine/rivastigmine plus memantine) are usually prescribed in secondary care and then continued by the GP after 3 months – with 1 post medication follow up visit or telephone call 6-12 weeks after initial prescription in most services). Current usual services are very light touch unless a patient has behavioural or social issues that require post diagnostic care. MCI patients usually receive no post diagnostic treatment,

	support or follow up. System change required for lecanemab and other disease modifying therapies offers an opportunity to diagnose and help people at an early disease stage, when independence could be maintained and quality of life can be optimised.
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Starting lecanemab will require i) biomarker confirmation of Alzheimer's disease (biomarker testing is not performed in most memory services), ii) clinical confirmation that the stage of disease is MCI or mild dementia (disease staging is part of current routine care), and iii) Pre-treatment MRI to exclude significant vascular disease (most patient do not currently have an MRI scan for diagnosis). Stopping rules are not clear and I think real-world outcomes are needed to guide/update stopping rules in the longer term. Current options for stopping include: i) to continue the treatment indefinitely in the long-term, ii) to stop the drug after 18 months (the duration of the trial), iii) to use amyloid PET reduction to below a threshold as an indicator that the drug can be stopped or iv) to use a clinical cut-off on a standard clinical measure below which the drug should be stopped (e.g. transition to moderate dementia). The problem with the penultimate option is that not all centres will have access to amyloid PET as they will be using CSF for diagnosis. I don't believe there is any clinical data to help choose between the other options and the most pragmatic/economically viable options are ii) and iv). Amyloid is likely to reaccumulate after lecanemab and other drugs in this class are stopped. An optimal patient pathway might include post treatment amyloid imaging/CSF and/or cognitive testing to determine whether there is re-accumulation and possibly decide to re-treat. Real world data collection would be vital to help nuance post-treatment clinical decision-making.
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?	The instruments for determining quality of life in dementia appear to be targeted to a later disease stage. I am concerned that they do not capture the impact of, for example, an isolated memory deficit that pervades many aspects of life (that require remembering to remember to carry out activities). Patients with MCI can usually wash, dress, move around, but due to memory loss their ability to work,

• 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	pursue their interests or enjoy anything with a prolonged narrative (book, TV series) is markedly affected. This can detrimentally affect quality of life without changing the score on a quality of life measure very much.
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 technology is a step-change. There is an unmet need to slow down Alzheimer's disease and delay the onset of dependency. Lecanemab has slowed down disease progression in Alzheimer's disease which is the essential facet of a technology that delays dependency.
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 side effects of note are infusion reactions that can require medication and Amyloid Related Imaging Abnormalities (ARIA). ARIA can be serious, but most of the time are asymptomatic. When they are serious symptoms include headache, confusion and seizures. If ARIA is confirmed on MRI, then lecanemab should be stopped at least temporarily. There would need to be significant training for clinicals on management of ARIA – this would involve dementia clinicians and also people working in Emergency Departments where patients may present with, for example, stroke-like episode. Extra MRIs would be required to manage ARIA.
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?	The diagnosis, drug administration and MRI monitoring in the lecanemab trial is all outside current usual NHS clinical practice. There are a few centres who do use biomarker-based diagnosis and perform MRI scans, but most do not. The primary outcomes of the trial were clinical with surrogate secondary outcomes. It is not clear to me if any of these surrogate outcomes could be used to predict clinical outcome (except apoE4 that was not an outcome measure itself but might predict clinical response).

• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	One adverse event that came to light after the trial was the death of a patient who was thrombolysed for stroke while taking lecanemab.
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
22. Are you aware of any new evidence for the comparator treatments since the publication of NICE technology appraisal guidance TA217?	No
23. How do data on real-world experience compare with the trial data?	We have not used lecanemab outside the trial setting.
24. 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	The trial was in people aged 50-90 years. This is a very wide range that covers most people with Alzheimer's but it is possible that older or younger people with Alzheimer's would be excluded from treatment if the label matches the trial entry criteria. As with all trials, patients with certain comorbidities were excluded – and therefore data are limited in these conditions. There are ethnic groups that were under-represented in the trial and therefore data are limited across some ethnicities. In clinical research generally, we recruit relatively low numbers of people from ethnic minority groups and our local experience suggests this is because we are seeing fewer people from ethnic minority groups in the early stages of dementia clinically. So, there is potential to exclude certain ethnicities from treatment if they are not accessing diagnostic service and nothing is done to mitigate this. Alzheimer's is very common in Down syndrome and I don't think people with Downs were included in the trials. Therefore I think clinicians may be reluctant to prescribe it without further data.

• 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.	In subgroup analyses of Clarity AD (lecanemab clinical trial), the clinical benefit was greater in men than women. There are sex differences in Alzheimer's prevalence and, probably, biology. Real-world data will be vital to understand whether there are real difference in the effectiveness of medication between sexes. To summarise, there are several potential inequities that could emerge in lecanemab delivery. The issue is more significant for lecanemab than with current care because there is no disease-modifying therapy currently – so people potentially miss out less from delaying diagnosis and treatment. New pathway development that will be required for lecanemab delivery is an opportunity to improve care for everyone.

Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

Lecanemab offers a modest but robust clinical benefit to patients with early clinical Alzheimer's disease within 18 months, and longer-term benefits such as maintaining independence, avoiding care home and hospital admissions are not yet known.

The current lack of disease-modifying therapies available for people with early Alzheimer's disease is devastating particularly for the people I see in my practice who are medically well otherwise, often economically active and still have a good quality of life.

Delivery of lecanemab will require a new patient pathway dedicated to diagnosis using biomarkers, administration of infusion and MRI imaging at predefined intervals as well as ad hoc in response to symptoms.

Blood biomarkers may open up the diagnostic process in future, but are not quite well enough validated yet to rely on for diagnosis.

Counselling patients about the risks and benefit of lecanemab will be important to help them make an informed treatment choice.

Thank you for your time.

Your privacy

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NICE National Institute for Health and Care Excellence

Single Technology Appraisal

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

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 mild cognitive impairment or mild dementia caused by Alzheimer's disease or caring for a patient with mild cognitive impairment or mild dementia caused by Alzheimer's disease. The text boxes will expand as you type.

In part 2 we are asking you to provide 5 summary sentences on the main points contained in this document.

Help with completing this form

If you have any questions or need help with completing this form please email the public involvement (PIP) team at pip@nice.org.uk (please include the ID number of your appraisal in any correspondence to the PIP team).

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.

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. Please type information directly into the form.

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Your response should not be longer than 15 pages.

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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.

Part 1: Living with this condition or caring for a patient with mild cognitive impairment or mild dementia caused by Alzheimer's disease

Table 1 About you, mild cognitive impairment or mild dementia caused by Alzheimer's disease, current treatments and equality

1. Your name	Larry G Woelk
2. Are you (please tick all that apply)	☒ A patient with mild cognitive impairment or mild dementia caused by Alzheimer's disease? ☒ A patient with experience of the treatment being evaluated? ☐ A carer of a patient with mild cognitive impairment or mild dementia caused by 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: Both my mother and my sister-in-law have had Alzheimer's with no apparent benefit from the drugs available at the time. I also have a close friend who is now diagnosed with Alzheimer's and is on medication. The decline in all three of these people has been markedly fast. Rita: my sister's Alzheimer's was a tragic thing to watch, complicated by a hip replacement and the prescription of pain meds that didn't help her situation at all. She was not on any medication initially and only started on Alzheimer's drugs when she went into a care home. She suffered multiple UTIs and a convulsion and was on stronger and stronger meds to control her behaviour. She has now been in a home for 10 years and is totally bed-ridden. She recognizes no one. ☐ 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 mild cognitive impairment or mild dementia caused by Alzheimer's disease? **If you are a carer (for someone with mild cognitive impairment or mild dementia caused by Alzheimer's disease) please share your experience of caring for them**	As a patient, my experience includes the occasional lapses in memory, anxiety caused by same, difficulty in absorbing information and decline in concentration. As a carer, I agree with all of the previous statement. I have very little to do with Larry's hygiene, dressing, exercise, driving, etc. Where I find my role is in taking care of the paperwork in our lives e.g. paying bills, filing taxes, etc.
7a. What do you think of the current treatments and care available for mild cognitive impairment or mild dementia caused by 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 have no experience of treatments available on the NHS as I have been fortunate enough to have been on the Lecanemab trial and extended Lecanemab for the past three years.** **When I compare my journey with those of friends, I have to say that I am maintaining a more normal lifestyle and will hope to continue as long as possible. The big difference that I notice is that I am quite conversational and**

	social where a good friend of mine seems quite isolated because he doesn't seem to remember what happened yesterday and therefore has no conversation.
8. If there are disadvantages for patients of current NHS treatments for mild cognitive impairment or mild dementia caused by Alzheimer's disease (for example, how they are given or taken, side effects of treatment, and any others) please describe these	Again, I have no direct experience or comparison of patients on current NHS treatments
9a. If there are advantages of lecanemab 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 lecanemab 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**	**Lecanemab has allowed me to carry on with my normal life, including all of my activities e.g. cycling, swimming, socializing, traveling, gardening, occasional cooking, driving and all my personal self-care.** **Being able to exercise which has always been part of my daily life, and remembering all of the bike routes I enjoy.** **I have no comment regarding any disadvantages of current treatments on the NHS as that is beyond my experience.**
10. If there are disadvantages of lecanemab over current treatments on the NHS please describe these. For example, are there any risks with lecanemab? If you are concerned about any potential side effects you have heard about, please describe them and explain why	I have not experienced any disadvantages with Lecanemab and cannot compare it to any available NHS treatments. I have not experienced any risks with Lecanemab nor have I experienced any side effects. My travel time to and from the hospital is around 3 hours but I take my bike with me and go for a ride through the New Forest after the infusion. The nursing staff at Lymington are marvelous and seem to find an appropriate vein each time I need an infusion and/or blood test. I have an MRI every few months and seem to be able to sleep through all the noise. I feel fortunate in that I have an outlet for any questions I have about this disease and I am comforted by the fact that that support is available.

11. Are there any groups of patients who might benefit more from lecanemab 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	From my experience, it is my belief that any patient suffering from Mild Cognitive Impairment would benefit from Lecanemab. The health screening before starting this trial was quite impressive and extensive. I had a full physical, EKG, PET scan and of course a full explanation of the pros and the cons of the drug. The previous trial I had been on, which was prematurely stopped, was just a pill. The infusion of this trial was much more of a commitment as I used to be needle-phobic. Of course not anymore.
12. Are there any potential equality issues that should be taken into account when considering mild cognitive impairment or mild dementia caused by Alzheimer's disease and lecanemab? 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.	I don't think any group of people would be excluded from Lecanemab due to equality issues.
13. Are there any other issues that you would like the committee to consider?	Having compared my journey, at a similar age as that of my sister-in-law, I can only state emphatically that my quality of life has been maintained for years longer than hers.

NICE National Institute for Health and Care Excellence

Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- Longer quality of life.
- Independent functionality
- Continuation of exercises
- Socializing
- Less anxiety

Thank you for your time.

Your privacy

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Erasmus School of Health Policy & Management

Maastricht University

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

Produced by Kleijnen Systematic Reviews (KSR) Ltd. in collaboration with Erasmus University Rotterdam (EUR) and Maastricht University

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Commercial in Confidence (CiC) data are highlighted in blue throughout the report.

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:

Marie Westwood acted as project lead and systematic reviewer on this assessment, critiqued the clinical effectiveness methods and evidence and contributed to the writing of the report. Sabine Grimm and Bram Ramaekers acted as health economic project leads, critiqued the company's economic evaluation and contributed to the writing of the report. Nigel Armstrong acted as health economist and systematic reviewer on this assessment, critiqued the company's clinical effectiveness evidence and economic evaluation and contributed to the writing of the report. Willem Witlox, Bradley Sugden, Teebah Abu-Zahra and Xiaoyu Tian acted as health economists on this assessment, critiqued the company's economic evaluation and contributed to the writing of the report. Kevin McDermott acted as a systematic reviewer, critiqued the clinical effectiveness methods and evidence and contributed to the writing of the report. Caro Noake critiqued the search methods in the submission and contributed to the writing of the report. Manuela Joore acted as health economist on this assessment, critiqued the company's economic evaluation, contributed to the writing of the report and provided general guidance.

Abbreviations

AAIC	Alzheimer's Association International Conference
AAN	American Academy of Neurology
Aβ	Amyloid beta
AChEi	Acetylcholinesterase inhibitor
AD	Alzheimer's disease
ADAS-Cog14	Alzheimer's Disease Assessment Scale-Cognitive subscale 14-item version
ADCOMS	Alzheimer's disease composite score
ADCS-ADL-MCI	Alzheimer's Disease Cooperative Study-Activities of Daily Living for use in Mild Cognitive Impairment
ADI	Alzheimer's Disease International
ADL	Activities of daily living
ADNI	Alzheimer's Disease Neuroimaging Initiative
AE	Adverse event
AIC	Akake Information Criterion
ANA	American Neurological Association
ApoE4	Apolipoprotein E4
ARIA	Amyloid-related imaging abnormality
ARIA-E	Amyloid-related imaging abnormality-oedema/effusion
ARIA-H	Amyloid-related imaging abnormality-microhaemorrhage and haemosiderin deposit
ARUK	Alzhemier's Research UK
BACE	β-site amyloid precursor protein cleaving enzyme
BIC	Bayesian Information Criterion
BNF	British National Formulary
CADTH	Canadian Agency for Drugs and Technologies in Health
CDR	Clinical Dementia Rating
CDR-SB	Clinical Dementia Rating scale – Sum of Boxes
CDSR	Cochrane Database of Systematic Reviews
CEA	Cost effectiveness analysis
CENTRAL	Cochrane Central Register of Controlled Trials
CI	Confidence interval
CRD	Centre for Reviews and Dissemination
CRF	Case report form
CRO	Contract research organisation
CS	Company submission
CSF	Cerebrospinal fluid
CSR	Clinical study report
C-SSRS	Columbia Suicide Severity Rating Scale
CTAD	Clinical Trials on Alzheimer's disease
CTCAE	Common Terminology Criteria for Adverse Events
DES	Discrete event simulation
DHSC	Department of Health and Social Care
DMT	Disease-modifying treatment
DSM	Diagnostic and Statistical Manual of Mental Disorders??
DSU	Decision Support Unit
EAG	Evidence Assessment Group
EAN	European Academy of Neurology
EMA	European Medicines Agency
eMIT	Electronic market information tool
EQ-5D	European Quality of Life-5 Dimensions
EQ-VAS	European Quality of Life – visual analogue scale
EUR	Erasmus University Rotterdam
FAQ	Functional Assessment Questionnaire

FAS	Full analysis set
FDA	Food and Drug Administration
FE	Fixing error
FLAIR	Fluid-attenuated inversion recovery
FV	Fixing violations
GDS	Global deterioration scale
GP	General practitioner
HES	Hospital Episode Statistics
HR	Hazard ratio
HRQoL	Health-related quality of life
HTA	Health Technology Assessment
iARDS	Integrated Alzheimer's disease rating scale
ICER	Incremental cost-effectiveness ratio
ICER	Institute for Clinical Economic Review
INR	International normalised ratio
IPECAD	International Pharmaco-Economic Collaboration on Alzheimer's Disease
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
ITT	Intention-to-treat
IV	Intravenous
Kg	kilogram
KSR	Kleijnen Systematic Reviews Ltd
LEC	Lecanemab
LEC10-BW	Lecanemab 10 mg/kg bi-weekly
LYG	Life-years gained
MCI	Mild cognitive impairment
MCID	Minimally clinically important difference
MedRA	Medical Dictionary for Regulatory Activities
MeSH	Medical Subject Headings
Mg	Milligram
MH	Microhaemorrhage
mITT	Modified intention-to-treat
MJ	Matters of judgement
MMRM	Mixed effects model with repeated measures
MMSE	Mini-mental state examination
MRI	Magnetic resonance imaging
N/A	Not applicable
NACC	National Alzheimer's Coordinating Center
NHB	Net health benefit
NHS	National Health Service
NHS EED	NHS Economic Evaluation Database
NIA-AA	National Institute on Aging and Alzheimer's Association
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health and Care Research
N/R	Not recorded
NYP	Not yet published
OLE	Open-label extension
OR	Odds ratio
OWSA	One-way sensitivity analysis
PAS	Patient Access Scheme
PBO	Placebo
PET	Positron emission tomography
PET-CT	Positron emission tomography-computed tomography
PD	Parkinson's disease
PRESS	Peer Review of Electronic Search Strategies
PRISMA	Preferred reporting items for systematic reviews and meta-analyses

PSA	Probabilistic sensitivity analysis
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
QALY	Quality-adjusted life year
QoL	Quality of life
QOL-AD	Quality of life in Alzheimer's disease
RCT	Randomised controlled trial
RePEc	Research Papers in Economics
SAE	Serious adverse event
SAS	Safety analysis set
SCI	Science Citation Index
SD	Standard deviation
SE	Standard error
SIGN	Scottish Intercollegiate Guideline Network
SLR	Systematic literature review
SmPC	Summary of product characteristics
SoC	Standard of care
SOP	Standard operating procedure
SS	Superficial siderosis
SUVR	Standardised uptake value ratio
TE	Treatment-emergent
TEAE	Treatment-emergent adverse event
TESAE	Treatment-emergent serious adverse event
TIA	Transient ischaemic attack
TPs	Transition probabilities
TRIP	Turning Research into Practice
TSD	Technical Support Document
Tx	Treatment
UK	United Kingdom
UMC+	University Medical Centre+
USA	United States of America
VAS	Visual analogue scale
WMS-IV LMII	Wechsler Memory Scale IV Logical Memory (subscale) II
ZBI	Zarit's Burden Interview

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1. EXECUTIVE SUMMARY

This summary provides a brief overview of the key issues identified by the Evidence Assessment Group (EAG) as being potentially important for decision making. If possible, 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 presents the key model outcomes. Section 1.3 discusses the decision problem, Section 1.4 issues relate to the clinical effectiveness, and Section 1.5 issues relate to the cost effectiveness. Other key issues are discussed in Section 1.6 while a summary is presented in Section 1.7.

Further information on the technology and evidence, and information on key as well as non-key issues are in the main EAG report, see Sections 2 (decision problem), 3 (clinical effectiveness), and 4 and 5 (cost effectiveness) for more details.

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 1.1: Summary of key issues

ID1457	Summary of issue	Report Sections
1	Need to test for Aβ disease to establish population eligible for lecanemab	2.1 and 4.2
2	Appropriateness of the SoC comparator for the MCI due to AD population	2.2, 2.3 and 3.2.6.1
3	Appropriateness of the SoC comparator for the mild dementia due to AD population	2.2, 2.3 and 3.2.6.1
4	Consideration of relevant clinical subgroups (specified in the NICE scope)	3.2.6.2
5	Lack of long-term data to support the clinical effectiveness of lecanemab	3.2.5
6	Uncertain clinical significance of the reported treatment effects	3.2.5
7	Applicability of the Clarity AD study to the UK setting	3.2.1 and 3.2.6.1
8	Uncertainty about the clinical effects of lecanemab by *ApoE4* genotype	3.2.6.2
9	Uncertainty about the requirements for MRI safety monitoring in relation to ARIA and variation by *ApoE4* genotype	3.2.2
10	Uncertainty about the clinical effects of lecanemab by patient age	3.2.6.2
11	Starting distribution of patients between MCI due to AD and mild AD in the economic model not in line with UK clinical practice	4.2.6
12	Possible methodological errors in estimation of and questionable validity of transition probabilities	4.2.6
13	Extrapolation of long-term treatment effect might be implausible	4.2.6
14	Mortality estimates in MCI due to AD state in the economic model are implausible	4.2.6
15	Uncertainty about treatment discontinuation in the economic model	4.2.6

ID1457	Summary of issue	Report Sections
16	Methodological uncertainty about approach to estimating utility, and potential face validity issues	4.2.8
17	Uncertainty in caregiver disutility due to patient institutionalisation	4.2.8
18	No AE disutilities applied	4.2.8
19	Cost and resource use discrepancies between the company's economic model and the NHS England Alzheimer's MCI model	4.2.9
20	Inclusion of health state costs outside the NHS and PSS perspective on costs	4.2.9
21	Inconsistency between estimated outcomes with the company model and observed data from Clarity AD	5.3

Aβ = amyloid beta; AD = Alzheimer's disease; AE = adverse event; *ApoE4* = apolipoprotein E4; ARIA = amyloid-related imaging abnormality; MCI = mild cognitive impairment; MRI = magnetic resonance imaging; NHS = National Health Service; NICE = National Institute for Health and Care Excellence; PSS = Personal Social Services; SoC = standard of care; UK = United Kingdom

The key differences between the company's preferred assumptions and the EAG's preferred assumptions resulted in these EAG changes in the model to yield the EAG base-case:

1. Change of patient baseline distribution mild cognitive impairment (MCI) due to Alzheimer's disease (AD)/mild AD to 38%/62%
2. Use standard of care (SoC) transition probabilities in (institution) mild AD/MCI due to AD health states
3. Disable severity-based stopping rule
4. Set mortality equal to that of general population in MCI due to AD health state
5. Use treatment-independent utility values
6. Disable caregiver institutionalisation disutility
7. Use National Health Service (NHS) England cost model estimates
8. Use diagnostic costs for all tested.

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.

Overall, the technology is modelled to affect QALYs by:

- Increased QALYs for lecanemab by increasing the number of patients staying at the MCI community stage, through slower disease progression and treatment-dependent utilities (QALY gain [redacted]).
- Increased life years gained (LYG) for lecanemab through slower disease progression (LY increased by [redacted] compared with SoC).

Overall, the technology is modelled to affect costs by:

- Increased acquisition costs (additional costs of £[redacted] compared with SoC)
- Increased administration costs (additional costs of £[redacted] compared with SoC)
- Increased monitoring costs (additional costs of £[redacted] compared with SoC)

- Increased test costs (additional costs of £[redacted] compared with SoC; note this increased in EAG base-case)
- Costs saving in direct non-medical care costs in the institutional care (cost saving of £[redacted] compared with SoC; note that this may be an over-estimate of the cost-saving).

The modelling assumptions that have the greatest effect on the ICER are:

- Modelling caregiver utility as the absolute quality of life (QoL) for both caregivers and patients summed in each cycle
- The baseline age was set to 60 years
- Switching to natural history data at baseline (0 years).

In addition, the EAG found that impactful modelling assumptions were:

- Using SoC transition probabilities for patients that discontinued treatment in MCI due to AD and mild AD
- The cost changes made based on the NHS England cost model
- Disabling the severity-based stopping rule.

1.3 The decision problem: summary of the EAG's key issues

The decision problem addressed in the company submission (CS) is broadly in line with the final scope issued by NICE. However, the definition of SoC with respect to the use of symptomatic pharmacological interventions (acetylcholinesterase inhibitors (AChEis) and/or memantine) differs from the final scope issued by NICE and may not be representative of UK clinical practice (Tables 1.2 and 1.3).

Table 1.2: Key issue 1: Need to test for Aβ disease to establish population eligible for lecanemab

Report Section	**2.1 and 4.2**
Description of issue and why the EAG has identified it as important	The population in the key clinical trial, Clarity AD, and of those eligible for lecanemab is narrower than that specified in the NICE final scope (although the economic analysis section of the scope does state "*the use of lecanemab is conditional on the presence of amyloid pathology"*), being defined by the presence of Aβ pathology, which requires one of the following: • CSF biomarker test • Amyloid PET scan This testing is not routinely used to diagnose AD. Therefore, a recommendation to use lecanemab will imply several consequences on cost and potentially health: • the cost of the testing • any harm to those tested, which includes more than those who would be eligible for lecanemab
What alternative approach has the EAG suggested?	Incorporating cost of testing
What is the expected effect on the cost effectiveness estimates?	ICER will increase.
What additional evidence or analyses might help to resolve this key issue?	Evidence as to the harm of any testing and its incorporation into the cost effectiveness analysis.

Report Section	2.1 and 4.2
Aβ = amyloid beta; AD = Alzheimer's disease; CSF = cerebrospinal fluid; EAG = Evidence Assessment Group; ICER = incremental cost-effectiveness ratio; NICE = National Institute for Health and Care Excellence; PET = positron emission tomography	

Table 1.3: Key issue 2: Appropriateness of the SoC comparator for the MCI due to AD population

Report Section	2.2, 2.3 and 3.2.6.1
Description of issue and why the EAG has identified it as important	The CS does not include any data about the comparative effects of lecanemab vs. non-pharmacological management (as specified in the NICE scope). This is because the key study (Clarity AD) was conducted in a mixed population (MCI due to AD and mild dementia due to AD) and over half of the patients in the study were receiving other pharmacological interventions for AD (AChEis and/or memantine). AChEis and memantine are not licensed for use in the MCI due to AD population and clinical expert opinion (sought by the EAG) has indicated that they are not routinely used, in this population, in UK clinical practice. The potential effects of concomitant treatment with AChEis and/or memantine on estimates of the treatment effects of lecanemab are unclear, e.g., active pharmacological treatment in the comparator group could reduce effect estimates, or a positive interaction effect between lecanemab and AChEis and/or memantine could increase treatment effect.
What alternative approach has the EAG suggested?	Provision of subgroup analyses for participants with MCI due to AD, who did not receive symptomatic AD medication (AChEi or memantine) during the study (Clarity AD). These analyses were requested at clarification and have been provided. When patients who received symptomatic AD medication (AChEi or memantine) were excluded, the adjusted mean difference in change from baseline, for lecanemab vs. placebo, at 18 months, for CDR-SB in the MCI subgroup, was reduced from -0.35, representing a 28% reduction in decline to [redacted], representing a [redacted]% reduction in decline. Information on the numbers of study participants, with MCI due to AD, who received symptomatic AD medication (AChEi or memantine) and non-pharmacological interventions was also requested and has been provided.
What is the expected effect on the cost effectiveness estimates?	The ICER [redacted] for all outcome measures.
What additional evidence or analyses might help to resolve this key issue?	The EAG considers that there is currently no further clinical effectiveness evidence available that could resolve this uncertainty. However, a cost effectiveness analysis for this subgroup still remains to be performed.
AD = Alzheimer's disease; AChEi = acetylcholinesterase inhibitor; CDR-SB = Clinical Dementia Rating scale – Sum of Boxes; CS = company submission; EAG = Evidence Assessment Group; ICER = incremental cost-effectiveness ratio; MCI = mild cognitive impairment; NICE = National Institute for Health and Care Excellence; SoC = standard of care; UK = United Kingdom	

Table 1.4: Key issue 3: Appropriateness of the SoC comparator for the mild dementia due to AD population

Report Section	2.2, 2.3 and 3.2.6.1
Description of issue and why the EAG has identified it as important	The decision problem specifies the comparator, for the mild dementia due to AD population, as AChEi plus non-pharmacological management (amended to AChEi and/or non-pharmacological management in the CS). As with Key issue 1 (see Table 1.2), these comparisons are not directly provided by the reported results of the Clarity AD study. UK clinical guidance (NG97) recommends the use of AChEis, but not memantine, in this population. Clinical expert opinion (sought by the EAG) has indicated that, in the UK, around 70% of people with mild AD dementia will take an AChEi and around 5% will take memantine. Potential undertreatment of the comparator group, for this population, could lead to overestimation of the effects of lecanemab. However, it should be noted that the percentage of patients in the mild subgroup of the Clarity AD trial who received AChEi was not that much less than 70%. Also, the treatment effect increased when patients treated with memantine were excluded.
What alternative approach has the EAG suggested?	Provision of subgroup analyses for participants with mild dementia due to AD, excluding: a) those participants who received memantine during the study (consistent with the company's definition of the decision problem); b) those patients who received memantine during the study and those patients who did not receive AChEi during the study (consistent with the NICE final scope). These analyses were requested at clarification; subgroup analyses excluding a) those participants who received memantine during the study, were provided. When patients who received memantine were excluded, the adjusted mean difference in change from baseline, for lecanemab vs. placebo, at 18 months, for CDR-SB in the mild dementia due to AD subgroup, was increased from -0.62, representing a 27% reduction in decline to [redacted], representing a [redacted]% reduction in decline. A possible alternative might be confirmation that the proportions of participants with mild dementia due to AD, in both arms of the Clarity AD study, who received treatment with an AChEi or memantine were consistent with UK clinical practice (e.g., 70% and 5% respectively, as indicated by clinical expert opinion. Additional information on the numbers of study participants, with mild dementia due to AD, who received symptomatic AD medication (AChEi or memantine) was provided.
What is the expected effect on the cost effectiveness estimates?	Unclear, but the difference will probably not be large if the clinical expert's estimate of AChEi use is correct.
What additional evidence or analyses might help to resolve this key issue?	The EAG considers that there is currently no further evidence available that could resolve this uncertainty.

Report Section	2.2, 2.3 and 3.2.6.1
AChEi = acetylcholinesterase inhibitor; AD = Alzheimer's disease; CDR-SB = Clinical Dementia Rating scale – Sum of Boxes; CS = company submission; EAG = Evidence Assessment Group; NICE = National Institute for Health and Care Excellence; SoC = standard of care; UK = United Kingdom	

Table 1.5: Key issue 4: Consideration of relevant clinical subgroups (specified in the NICE scope)

Report Section	3.2.6.2
Description of issue and why the EAG has identified it as important	Subgroups specified in the NICE final scope were: apolipoprotein E4 (*ApoE4*) gene carrier status; MCI due to AD; mild dementia due to AD. Clinical effectiveness subgroup analyses were provided in Appendix E of the CS. Cost effectiveness modelling included scenario analyses considering MCI due to AD mild dementia due to AD populations separately, however, no scenarios based on *ApoE4* gene carrier status were presented.
What alternative approach has the EAG suggested?	Implementation of scenario analysis for *ApoE4* gene carrier status, considering non-carrier, heterozygote and homozygote. These analyses were requested and performed by the company at clarification.
What is the expected effect on the cost effectiveness estimates?	ICER decreases in non-carriers and increases in carriers, [redacted] in the homozygous group.
What additional evidence or analyses might help to resolve this key issue?	No other evidence required.
AD = Alzheimer's disease; *ApoE4* = apolipoprotein E4; CS = company submission; EAG = Evidence Assessment Group; ICER = incremental cost-effectiveness ratio; MCI = mild cognitive impairment; NICE = National Institute for Health and Care Excellence	

1.4 The clinical effectiveness evidence: summary of the EAG's key issues

The EAG identified five major concerns with the evidence presented on the clinical effectiveness: short (in the context of AD) follow-up (18-months) provided by the key study (Clarity AD) (Table 1.6); uncertain clinical significance of the observed treatment effects of lecanemab (Table 1.7); applicability of the Clarity AD study to the UK setting (Table 1.8); uncertainty about the effectiveness of lecanemab treatment for some subgroups, homozygote apolipoprotein E4 (*ApoE4)* gene carriers (Table 1.9), patients under 65 years of age (Table 1.11) and patients with MCI due to AD who are not receiving concomitant symptomatic AD treatments (Table 1.8); uncertainty about the appropriate criteria for suspension of treatment due to amyloid-related imaging abnormality (ARIA) and about the extent of additional magnetic resonance imaging (MRI) safety monitoring likely to be required as a result of such treatment suspensions (Table 1.10).

Table 1.6: Key issue 5: Lack of long-term data to support the clinical effectiveness of lecanemab

Report Section	3.2.5
Description of issue and why the EAG has identified it as important	Clinical effectiveness data, included in the CS, are limited to the results of one RCT (Clarity AD) with a follow-up duration of 18-months. Given the nature of the condition and of the intervention (lecanemab is a disease-modifying treatment, rather than a treatment of symptoms), 18-months follow-up is unlikely to

Report Section	3.2.5
	sufficient to adequately assess treatment effects; for example, any observed initial delay in disease progression may not extrapolate to long-term benefit if the delay in progression does not remain constant and persist beyond 18 months.
What alternative approach has the EAG suggested?	Provision of long-term outcome data – there is an OLE to Clarity AD (6 to 48 months), which is ongoing. In its clarification response, the company provided some initial (24-month) results from the OLE. The EAG considers that currently available data are insufficient to adequately demonstrate the long-term efficacy of lecanemab.
What is the expected effect on the cost effectiveness estimates?	Unclear.
What additional evidence or analyses might help to resolve this key issue?	The EAG considers that there is currently no further evidence available that could resolve this uncertainty.
AD = Alzheimer's disease; CS = company submission; EAG = Evidence Assessment Group; OLE = open-label extension; RCT = randomised controlled trial	

Table 1.7: Key issue 6: Uncertain clinical significance of the reported treatment effects

Report Section	3.2.5
Description of issue and why the EAG has identified it as important	The Clarity AD trial reported that patients treated with lecanemab experienced smaller changes from baseline than those in the placebo group, for all six cognition and function domains of the CDR-SB (the primary outcome measure), however, the absolute difference in change between the treatment and placebo groups was small. Studies cited (references 183 and 186 in the CS) in support of the clinical significance of the treatment effect indicate that an increase of between 1 and 2 points on CDR-SB would be considered a clinically significant decline; the reported adjusted mean between group difference in change from baseline was -0.451 over 18 months. Neither the core Clarity AD study nor the OLE include collection of data on key clinical end points, e.g., admission to full-time care (included in the NICE final scope). Clinical expert opinion (sought by the EAG) regarding what % reduction in decline would be considered clinically meaningful: *"This is problematic and likely to be different at different disease stages. Importantly, Individual patients/families will have very different views on what is meaningful for them, depending on their differing values and expectations. When deciding whether to prescribe lecanemab, I would be strongly influenced by their views in each individual case. I think somewhere between 20 and 40% would apply for most people and so sounds about right to me, but this benefit would have to outweigh treatment burden and risks. In oncology, a 20-30% benefit in the right direction seems to be considered clinically meaningful without any question.*

Report Section	3.2.5
	The absolute difference of 0.45 on CDR-SB is about the same as achieved by existing anticholinesterase drugs for AD (that are symptomatic rather than influencing rate of decline) and most people now believe their benefit is clinically meaningful. This is despite the size of effect being less than the cited minimum clinically important difference of >1." Studies cited in the CS, in support of the clinical significance of the treatment effect indicate that an increase of between 1 and 2 points on CDR-SB would be considered a clinically significant decline; the reported adjusted mean between group difference in change from baseline was -0.451 over 18 months.
What alternative approach has the EAG suggested?	None.
What is the expected effect on the cost effectiveness estimates?	Unclear.
What additional evidence or analyses might help to resolve this key issue?	Collection of data, ideally long-term (>18 months), on e.g., time to admission to full-time care, time to progression to moderate or severe AD. The EAG considers that there is currently no further evidence available that could resolve this uncertainty.
AD = Alzheimer's disease; CDR-SB = Clinical Dementia Rating scale – Sum of Boxes; CS = company submission; EAG = Evidence Assessment Group; NICE = National Institute for Health and Care Excellence; OLE = open-label extension	

Table 1.8: Key issue 7: Applicability of the Clarity AD study to the UK setting

Report Section	3.2.1 and 3.2.6.1
Description of issue and why the EAG has identified it as important	The CSR indicates that [redacted] UK patients were included in the Clarity AD study. The CS indicates that approximately [redacted]% of participants in the Clarity AD study had MCI at baseline and approximately [redacted]% had mild AD. Clinical expert opinion (sought by the EAG) has indicated that; *"In the UK, patients are currently more likely to present at the mild dementia than MCI stage, and so the proportions offered lecanemab might be reversed (i.e. [redacted]% MCI, [redacted]% dementia)."* Clinical expert opinion (sought by the EAG) has indicated that the proportions of participants in the Clarity AD study (particularly in respect of the population with MCI due to AD) who received concomitant treatment with an AChEi and/or memantine is unlikely to be consistent with current UK clinical practice. Clinical expert opinion (sought by the EAG) has indicated that, whilst CDR-SB is an accepted outcome measure in clinical trials, it is not routinely used on clinical practice due to resource requirements (20-30 minute structured interview conducted by a trained clinician). CDR-SB, to establish disease stage, was part of the inclusion criteria for the Clarity AD study; a change in UK clinical practice, with respect to the staging of AD, may therefore be needed in order to ensure the selection of appropriate patients for treatment with lecanemab.

Report Section	3.2.1 and 3.2.6.1
What alternative approach has the EAG suggested?	Provision of evidence about the rates of treatment with AChEis and memantine, in the UK, of patients with MCI due to AD and mild dementia due to AD, and/or provision of appropriate subgroup analyses. Both information about the rates of treatment with AChEis and memantine, in the UK, of patients with MCI due to AD and mild dementia due to AD, and subgroup analyses were provided in the clarification response. The EAG considers that (with the exception of the use of AChEis in the mild AD subgroup), the concomitant use of symptomatic AD medication (AChEis and memantine) in the Clarity AD study was unlikely to reflect UK clinical practice; the apparent discrepancy is most notable with respect to the management of patients with MCI due to AD. In addition, the EAG considers that the results of the subgroup analyses raise a question about whether lecanemab has a clinically significant effect, in patients with MCI due to AD, when used in the context of UK SoC (i.e., without concomitant symptomatic AD treatment); The adjusted mean difference in change from baseline, for lecanemab vs. placebo, at 18 months, for CDR-SB in this subgroup, was [redacted], representing a [redacted]% reduction in decline. Consideration of the potential costs of standardising methods used to AD stage.
What is the expected effect on the cost effectiveness estimates?	Unclear.
What additional evidence or analyses might help to resolve this key issue?	The EAG considers that there is currently no further evidence available that could resolve this uncertainty.
AChEi = acetylcholinesterase inhibitor; AD = Alzheimer's disease; CDR-SB = Clinical Dementia Rating scale – Sum of Boxes; CS = company submission; CSR = clinical study report; EAG = Evidence Assessment Group; MCI = mild cognitive impairment; SoC = standard of care; UK = United Kingdom	

Table 1.9: Key issue 8: Uncertainty about the clinical effects of lecanemab by *ApoE4* genotype

Report Section	3.2.6.2
Description of issue and why the EAG has identified it as important	Subgroup analyses of data from the Clarity AD study (reported in appendix E of the CS) indicate a substantial variation in treatment effect, for the primary outcome measure (CDR-SB), with *ApoE4* genotype: non-carriers (n=542), adjusted mean difference in change from baseline -0.75 (41% slowing of decline); heterozygote (n=924), adjusted mean difference in change from baseline -0.50 (30% slowing of decline); homozygote (n=268), adjusted mean difference in change from baseline 0.28 (22% faster decline, confidence interval including no effect).
What alternative approach has the EAG suggested?	Implementation of scenario analysis for *ApoE4* gene carrier status, considering non-carrier, heterozygote and homozygote. These analyses were requested at clarification.

Report Section	3.2.6.2
What is the expected effect on the cost effectiveness estimates?	Unclear.
What additional evidence or analyses might help to resolve this key issue?	Collection of more data to inform the possible variation of treatment efficacy by genotype, particularly with respect to the *ApoE4* homozygote population. The EAG considers that there is currently no further evidence available that could resolve this uncertainty.

AD = Alzheimer's disease; *ApoE4* = apolipoprotein E4; CDR-SB = Clinical Dementia Rating scale – Sum of Boxes; CS = company submission; EAG = Evidence Assessment Group

Table 1.10: Key issue 9: Uncertainty about the requirements for MRI safety monitoring in relation to ARIA and variation by *ApoE4* genotype

Report Section	3.2.2
Description of issue and why the EAG has identified it as important	The appropriate frequency for MRI safety monitoring is unclear, particularly in relation to additional MRI scans and clinical assessments that may be required, before resumption of treatment, in patients in whom lecanemab treatment has been suspended due to ARIA. There is also some uncertainty around what ARIA-related criteria are recommended to trigger suspension of dosing and what criteria were applied in the Clarity AD study. There appears to be some inconsistency between the reported treatment suspension criteria used in Clarity AD and [redacted] Higher rates of ARIA have been observed in both the heterozygous and homozygous *ApoE4* carrier populations, compared to non-carriers; it is unclear whether safety monitoring requirements should vary by *ApoE4* genotype. The draft SmPC includes the following statement: [redacted]

Report Section	3.2.2
What alternative approach has the EAG suggested?	Provision of more detail about safety monitoring undertaken during the Clarity AD study (completed in response to clarification questions A22 and A23). Provision of data on adverse events of special interest (primarily ARIA) by *ApoE4* genotype subgroup (provided in response to clarification question A9).
What is the expected effect on the cost effectiveness estimates?	ICER will likely decrease in non-carriers and increase in carriers.
What additional evidence or analyses might help to resolve this key issue?	Provision of more detail about safety monitoring undertaken during the Clarity AD study (Clarification question A23). Provision of data on adverse events of special interest (primarily ARIA) by *ApoE4* genotype subgroup.
AD = Alzheimer's disease; *ApoE4* = apolipoprotein E4; ARIA = amyloid-related imaging abnormalities; EAG = Evidence Assessment Group; MRI = magnetic resonance imaging; SmPC = summary of product characteristics	

Table 1.11: Key issue 10: Uncertainty about the clinical effects of lecanemab by patient age

Report Section	3.2.6.2
Description of issue and why the EAG has identified it as important	Subgroup analyses of data from the Clarity AD study (reported in appendix E of the CS) indicate a possible relationship between treatment effect, for the primary outcome measure (CDR-SB), and patient age: ≥75 years (n=641), adjusted mean difference in change from baseline -0.72 (40% slowing of decline); 65-74 years (n=749), adjusted mean difference in change from baseline -0.37 (23% slowing of decline); <65 years (n=344), adjusted mean difference in change from baseline -0.08 (6% slowing of decline, confidence interval including no effect).
What alternative approach has the EAG suggested?	None.
What is the expected effect on the cost effectiveness estimates?	Unclear.
What additional evidence or analyses might help to resolve this key issue?	Collection of more data to inform the possible variation of treatment efficacy with patient age. The EAG considers that there is currently no further evidence available that could resolve this uncertainty.
AD = Alzheimer's disease; CDR-SB = Clinical Dementia Rating scale – Sum of Boxes; CS = company submission; EAG = Evidence Assessment Group	

1.5 The cost effectiveness evidence: summary of the EAG's key issues

Table 1.12: Key issue 11: Starting distribution of patients between MCI due to AD and mild AD in the economic model

Report Section	4.2.6
Description of issue and why the EAG has identified it as important	The proportions of patients who have MCI due to AD or mild AD used in the model are not in line with what is likely seen in UK clinical practice.

What alternative approach has the EAG suggested?	Use proportions in line with EAG clinical expert opinion.
What is the expected effect on the cost effectiveness estimates?	The EAG's change increases the ICER.
What additional evidence or analyses might help to resolve this key issue?	Formal elicitation of expert opinion.
AD = Alzheimer's disease; EAG = Evidence Assessment Group; ICER = incremental cost-effectiveness ratio; MCI = mild cognitive impairment; UK = United Kingdom	

Table 1.13: Key issue 12: Possible methodological errors in estimation of and questionable validity of transition probabilities

Report Section	**4.2.6**
Description of issue and why the EAG has identified it as important	There are three key uncertainties surrounding transition probabilities: • Appropriateness of backward transitions • The use of time-dependent transition probabilities may be more appropriate • Best practices not followed for estimation of transition probabilities under competing risks
What alternative approach has the EAG suggested?	• Disable backward transitions in scenario • Perform further validation (such as CS Tables 71-74) on the use of the time-dependent transition probabilities derived using the multistate model; explain how competing risks were handled in the multistate approach • Explore approach 1 detailed in tutorial by Gidwani et al
What is the expected effect on the cost effectiveness estimates?	• The EAG's change increases the ICER. • Decreases ICER according to company scenario, but may increase ICER using other distributions (e.g., generalised gamma) • Unclear
What additional evidence or analyses might help to resolve this key issue?	The EAG would be interested in how competing risks were handled in the multistate analysis and whether the company consider this analysis more appropriate than the original approach to estimating transition probabilities.
CS = company submission; EAG = Evidence Assessment Group; ICER = incremental cost-effectiveness ratio	

Table 1.14: Key issue 13: Effectiveness – Extrapolation of long-term treatment effect might be implausible

Report Section	**4.2.6**
Description of issue and why the EAG has identified it as important	Long-term treatment effect based on assumptions: the hazard ratio estimated from the trial holds throughout model time horizon for patients on treatment (and those discontinued in MCI due to AD and mild AD states)
What alternative approach has the EAG suggested?	• Explore treatment effect waning scenarios

	• Off-treatment patients in MCI due to AD/mild AD should have transition probabilities of SoC, not lecanemab
What is the expected effect on the cost effectiveness estimates?	• Not explored, but will increase the ICER. • The EAG's change increases the ICER.
What additional evidence or analyses might help to resolve this key issue?	Explore treatment effect waning scenarios over time. Provide further information regarding how the numbers of patients in the modelled off-treatment MCI due to AD and mild AD states compare to those in the observed off-treatment MCI due to AD and mild AD states in Clarity AD. Provide further explanation on the appropriateness of assuming no reduction in the lecanemab treatment effect on treatment and in the lecanemab arm off-treatment MCI due to AD and mild AD health states in the long term, given that: • the treatment effect was estimated based on all patients in the trial, most of whom were on treatment (only 17.9% discontinued), so it cannot be applicable to patients off-treatment • patients discontinue at potentially different rates beyond the end of study follow-up • even on treatment, the treatment effect might reduce with time
AD = Alzheimer's disease; EAG = Evidence Assessment Group; ICER = incremental cost-effectiveness ratio; MCI = mild cognitive impairment; SoC = standard of care	

Table 1.15: Key issue 14: Mortality estimates in MCI due to AD state are implausible

Report Section	**4.2.6**
Description of issue and why the EAG has identified it as important	Mortality estimates in the model are below those of the general population for patients with MCI due to AD, which lacks face validity.
What alternative approach has the EAG suggested?	• Set mortality equal to general population in MCI due to AD health state.
What is the expected effect on the cost effectiveness estimates?	• The EAG's change increases the ICER.
What additional evidence or analyses might help to resolve this key issue?	As above.
AD = Alzheimer's disease; EAG = Evidence Assessment Group; ICER = incremental cost-effectiveness ratio; MCI = mild cognitive impairment	

Table 1.16: Key issue 15: Uncertainty about treatment discontinuation in the economic model

Report Section	**4.2.6**
Description of issue and why the EAG has identified it as important	Treatment discontinuation may be over-estimated in the model due to all-cause discontinuation rate assumed constant in trial and beyond; and potential double-counting of all-cause discontinuation and stopping rules. The appropriateness of the severity-based and institutionalisation-based stopping rules is still unclear.

What alternative approach has the EAG suggested?	• Explore no or reduced all-cause treatment discontinuation beyond 18 months. • And / or disable severity-based stopping rule • Disable institutionalisation-based stopping rule in scenario
What is the expected effect on the cost effectiveness estimates?	• The EAG's change increases the ICER. • The EAG's change increases the ICER. • The EAG's change increases the ICER.
What additional evidence or analyses might help to resolve this key issue?	As above. Provide further expert opinion on the appropriateness and operationalisation of stopping rules in practice.
EAG = Evidence Assessment Group; ICER = incremental cost-effectiveness ratio	

Table 1.17: Key issue 16: Methodological uncertainty about approach to estimating utility, and potential face validity issues

Report Section	**4.2.8**
Description of issue and why the EAG has identified it as important	Utility values for the MCI due to AD and mild AD health states were calculated as the mean EQ-5D values across all (post-)baseline observations. The approach does not consider within/between-patient variability, ignores potential confounding variables and potentially oversimplifies results through not capturing changes to utility over time. Derived utilities are treatment dependent which cannot be reasonably justified within the current approach. These utility values for the MCI due to AD and mild AD health states are higher than the UK age and gender matched general population utilities. The EAG thus questions the face validity of the results. When applying utilities in the model, utility decrements were additively applied, deviating from best practice recommendations in NICE DSU TSD 12.
What alternative approach has the EAG suggested?	The EAG propose an alternative approach (i.e., mixed effects model) to account for potential confounding variables, and to handle variability within and between patients over time. The approach can further be used to assess the plausibility of treatment-dependent utilities. Handling of missing data should be clearly reported and justified. When applying utility decrements, a multiplicative approach should be used. In a scenario, utility values were capped for the MCI due to AD and mild AD health states, which subsequently impacts the moderate and severe AD health state utility values.
What is the expected effect on the cost effectiveness estimates?	Unclear. The scenario capping utility values increased the ICER.
What additional evidence or analyses might help to resolve this key issue?	To derive utility values for the MCI due to AD and mild AD health states using an alternative approach (i.e., mixed effects model). When applying utility decrements, a multiplicative approach should be used. Handling of missing data should be clearly reported and justified. The impact of capping or adjusting by general population utility values should be explored.
AD = Alzheimer's disease; DSU = Decision Support Unit; EAG = Evidence Assessment Group; EQ-5D = European Quality of Life-5 Dimensions; ICER = incremental cost-effectiveness ratio; MCI = mild cognitive	

Report Section	4.2.8
impairment; NICE = National Institute for Health and Care Excellence; TSD = technical support document; UK = United Kingdom	

Table 1.18: Key issue 17: Uncertainty in caregiver disutility due to patient institutionalisation

Report Section	4.2.8
Description of issue and why the EAG has identified it as important	The CS applied a disutility of 0.09 to capture the impact of patient institutionalisation on caregiver HRQoL. As per consultation with a clinical expert, in addition to the conflicting results from Verbeek et al. with Farina et al[1], the impact of institutionalisation on caregiver utilities remains unclear to the EAG.
What alternative approach has the EAG suggested?	The EAG disabled the caregiver utility decrement with institutionalisation in its base-case.
What is the expected effect on the cost effectiveness estimates?	The ICER increased.
What additional evidence or analyses might help to resolve this key issue?	None.
CS = company submission; EAG = Evidence Assessment Group; HRQoL = health-related quality of life; ICER = incremental cost-effectiveness ratio	

Table 1.19: Key issue 18: No AE disutilities applied

Report Section	4.2.8
Description of issue and why the EAG has identified it as important	No AE disutilities were applied in the model, despite HRQoL measures only being administered every six months and AEs of special interest typically being resolved within four months. This is likely to overestimate health state utility values, failing to capture the impact of AEs on HRQoL. Upon request, the company provided a scenario analysis including AE disutilities. However, the scenario seemingly underestimated the duration of AEs, underestimated the disutility for grade 3+ infusion-related reactions, and did not incorporate AE disutilities for grade 1 and 2 ARIA AEs. This is likely to result in the impact of AEs on HRQoL not being fully captured.
What alternative approach has the EAG suggested?	The EAG requested a scenario analysis incorporating AE disutilities, which it has adopted in its base case. The EAG recommends an additional scenario analysis, using more realistic AE durations, using alternative AE disutilities for grade 3+ infusion-related reactions, and applying AE disutilities to grade 1 and 2 ARIA AEs.
What is the expected effect on the cost effectiveness estimates?	The scenario provided by the company resulted in a PAS ICER of [redacted]. The suggested analysis is likely to further increase the ICER.
What additional evidence or analyses might help to resolve this key issue?	The EAG recommends an additional scenario analysis, using more realistic AE durations, using alternative AE disutilities for grade 3+ infusion-related reactions, and applying AE disutilities to grade 1 and 2 ARIA AEs.

Report Section	4.2.8
AE = adverse event; ARIA = amyloid-related imaging abnormalities; EAG = Evidence Assessment Group; HRQoL = health-related quality of life; ICER = incremental cost-effectiveness ratio; PAS = patient access scheme	

Table 1.20: Key issue 19: Cost and resource use discrepancies between the company's economic model and the NHS England Alzheimer's MCI model

Report Section	4.2.9
Description of issue and why the EAG has identified it as important	Cost and resource use disparities were identified between the company's economic model and the NHS England Alzheimer's MCI model, including differences in unit costs, MRI safety monitoring, Aβ and *ApoE4* testing, GP visits, quarterly outpatient reviews, and referral to local services
What alternative approach has the EAG suggested?	• The EAG adopted the IV infusion administration, lumbar puncture and PET-CT unit costs from the NHS England Alzheimer's MCI model in its base-case. • The EAG included 4 MRIs in the first year and 2 MRIs in every year thereafter for the modelling of lecanemab safety monitoring, in line with the NHS England Alzheimer's MCI model and the EAGs clinical expert comments. • The EAG performed a scenario analysis including *ApoE4* test costs.
What is the expected effect on the cost effectiveness estimates?	• The ICER increased with these changes.
What additional evidence or analyses might help to resolve this key issue?	An updated economic model including costs of GP visits, quarterly outpatients' reviews, *ApoE4* testing and referral to local services.
Aβ = amyloid beta; *ApoE4* = apolipoprotein E4; EAG = Evidence Assessment Group; GP = general practitioner; ICER = incremental cost-effectiveness ratio; IV = intravenous; NHS = National Health Service; MCI = mild cognitive impairment; MRI = magnetic resonance imaging; PET-CT = positron emission tomography-computed tomography	

Table 1.21: Key issue 20: Inclusion of health state costs outside the NHS and PSS perspective on costs

Report Section	4.2.9
Description of issue and why the EAG has identified it as important	Direct non-medical costs in the company's economic model included private care costs that fall outside the NHS and PSS perspective on costs
What alternative approach has the EAG suggested?	Exclude any costs outside of the NHS and PSS perspective on costs.
What is the expected effect on the cost effectiveness estimates?	Based on the company's scenario analysis in response to clarification question B24, the ICER is expected to increase.
What additional evidence or analyses might help to resolve this key issue?	A different source to inform health state costs (if available), that includes a more transparent breakdown of the different cost components

Report Section	4.2.9
EAG = Evidence Assessment Group; ICER = incremental cost-effectiveness ratio; NHS = National Health Service; PSS = Personal Social Services	

Table 1.22: Key issue 21: Inconsistency between estimated outcomes with the company model and observed data from Clarity AD

Report Section	5.3
Description of issue and why the EAG has identified it as important	In CS Tables 71 and 72 a comparison with the CS model and Clarity AD was made with regards to health state occupancy over time. The 18-month health state occupancy for the "Severe AD" health state is substantially overestimated. In response to clarification question B28, the company acknowledged "*that the health state occupancy for the 'Severe AD' state is over-estimated in both the lecanemab and SoC arms of the model compared with the observed occupancy in Clarity AD*".
What alternative approach has the EAG suggested?	See below.
What is the expected effect on the cost effectiveness estimates?	From clarification response Table 76 it becomes clear that the economic model systematically overestimates the lecanemab benefits compared with Clarity AD in terms of health state occupancy in the moderate AD, severe AD and death health states.
What additional evidence or analyses might help to resolve this key issue?	Based on the current assessment, the EAG considers that the company's economic model does not accurately predict the state occupancy as observed in Clarity AD for both treatments and that there is a potential bias favouring the effectiveness of lecanemab. This might be related to the issue raised by the EAG in clarification question B10, i.e., potential technical errors in the estimation of transition probabilities to multiple health states and their conversion to a different period length matching the cycle length. Hence, this error should be corrected and subsequently the validation assessment be repeated.
AD = Alzheimer's disease; CS = company submission; EAG = Evidence Assessment Group; SoC = standard of care	

1.6 Other key issues: summary of the EAG's view

Not applicable.

1.7 Summary of the EAG's view

Table 1.23: Summary of EAG's preferred assumptions and ICER

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
CS base-case					
Lecanemab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SoC	[redacted]	[redacted]			
1. Patient baseline distribution MCI/mild AD changed to 38%/62%					
Lecanemab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SoC	[redacted]	[redacted]			

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
2. Off-treatment (community and institution) mild/MCI states should have SoC TPs					
Lecanemab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SoC	[redacted]	[redacted]			
3. Disable severity-based stopping rule					
Lecanemab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SoC	[redacted]	[redacted]			
4. Mortality in MCI set HR=1					
Lecanemab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SoC	[redacted]	[redacted]			
5. Use treatment-independent utility values					
Lecanemab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SoC	[redacted]	[redacted]			
6. Disable caregiver institutionalisation disutility					
Lecanemab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SoC	[redacted]	[redacted]			
7. NHS cost model changes					
Lecanemab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SoC	[redacted]	[redacted]			
8. Diagnostic costs for all tested					
Lecanemab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SoC	[redacted]	[redacted]			
EAG base-case					
Lecanemab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SoC	[redacted]	[redacted]			

AD = Alzheimer's disease; CS = company submission; EAG = Evidence Assessment Group; HR = hazard ratio; ICER = incremental cost-effectiveness ratio; NHS = National Health Service; MCI = mild cognitive impairment; QALY = quality-adjusted life year; SoC = standard of care; TPs = transition probabilities
Results deterministic unless indicated.

Table 1.24: Summary of EAG's scenario analysis results

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
EAG base-case					
Lecanemab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SoC	[redacted]	[redacted]			
1. Disable all-cause tx discontinuation after trial period					
Lecanemab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SoC	[redacted]	[redacted]			
2. Disable all-cause tx discontinuation after trial period but enable severity-based stopping rule					
Lecanemab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SoC	[redacted]	[redacted]			
3. Disable institutionalisation-based stopping rule scenario					
Lecanemab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SoC	[redacted]	[redacted]			
4. Backward transitions disabled					
Lecanemab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
SoC	[redacted]	[redacted]			
5. Use pessimistic imputation (assume missing=moderate) for transition probability analysis					
Lecanemab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SoC	[redacted]	[redacted]			
6. Multistate survival analysis transition probabilities					
Lecanemab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SoC	[redacted]	[redacted]			
7. Mortality estimates informed by Potashman et al					
Lecanemab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SoC	[redacted]	[redacted]			
8. Cap utility values at general population values					
Lecanemab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SoC	[redacted]	[redacted]			
9. Assume 2/3 of direct non-medical are private costs					
Lecanemab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SoC	[redacted]	[redacted]			
Results deterministic unless indicated. EAG = Evidence Assessment Group; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life year; SoC = standard of care; tx = treatment					

Table 1.25: Summary of EAG's subgroup results

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
EAG base-case					
Lecanemab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SoC	[redacted]	[redacted]			
MCI due to AD					
Lecanemab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SoC	[redacted]	[redacted]			
Mild AD					
Lecanemab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SoC	[redacted]	[redacted]			
***APoE4* non-carriers**					
Lecanemab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SoC	[redacted]	[redacted]			
***APoE4* homozygotes**					
Lecanemab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SoC	[redacted]	[redacted]			
***APoE4* heterozygotes**					
Lecanemab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SoC	[redacted]	[redacted]			
Results deterministic unless indicated. AD = Alzheimer's disease; *ApoE4* = apolipoprotein E4; EAG = Evidence Assessment Group; ICER = incremental cost-effectiveness ratio; MCI = mild cognitive impairment; QALY = quality-adjusted life year; SoC = standard of care					

2. CRITIQUE OF COMPANY'S DEFINITION OF DECISION PROBLEM

Table 2.1: Statement of the decision problem (as presented by the company)

	Final scope issued by NICE	Decision problem addressed in the CS	Rationale if different from the final NICE scope	EAG Comment
Population	People with MCI or mild dementia due to AD.	People with MCI or mild dementia due to AD.	N/A – in line with the NICE final scope.	The population is in line with the NICE scope.
Intervention	Lecanemab plus established clinical management.	Same as scope (see below for established clinical management).	N/A – The CS stated that the intervention was in line with the NICE final scope.	It is not clear that the concomitant treatments, used in both the lecanemab and placebo arms of the Clarity AD trial (the key source of clinical effectiveness estimates for the CS), were consistent with 'established clinical management' in the UK. In the lecanemab arm of the Clarity AD trial (the key source of clinical effectiveness estimates for the CS), [redacted] participants were reported to be taking at least one concomitant AD medication, and [redacted] were reported to be taking memantine. In the placebo arm of the Clarity AD trial (the key source of clinical effectiveness estimates for the CS), [redacted] participants were reported to be taking at
Comparator(s)	Established clinical management without lecanemab, including, but not limited to: • For MCI due to AD, non-pharmacological management • For mild dementia due to AD, an AChEi plus non-pharmacological management	Established clinical management without lecanemab as, including, but not limited to: • For MCI due to AD, non-pharmacological management • For mild dementia due to AD, an AChEi and/or non-pharmacological management These data were not reported separately for patients with MCI due to AD and those with mild dementia due to AD.	The CS stated that, for patients with mild dementia dues to AD, the comparator was *"changed from plus non-pharmacological management to and/or non-pharmacological management" to align with the Clarity AD trial and UK guidelines for dementia."*	

	Final scope issued by NICE	Decision problem addressed in the CS	Rationale if different from the final NICE scope	EAG Comment
				least one concomitant AD medication, and [redacted] were reported to be taking memantine. These data were not reported separately for patients with MCI due to AD and those with mild dementia due to AD. It is not clear that the concomitant treatments, used in both the lecanemab and placebo arms of the Clarity AD trial (the key source of clinical effectiveness estimates for the CS), were consistent with 'established clinical management' in the UK.

	Final scope issued by NICE	Decision problem addressed in the CS	Rationale if different from the final NICE scope	EAG Comment
Outcomes	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 • HRQoL • Adverse effects of treatment	The CS included measures of cognitive and functional impairment, HRQoL and adverse effects.	N/A – The CS stated that the intervention was in line with the NICE final scope.	The CS did not include data on ability to remain independent, admission to full-time care or non-cognitive symptoms (e.g., behavioural and psychiatric symptoms).
Economic analysis				
Subgroups to be considered	If the evidence allows the following subgroups will be considered: • *ApoE4* gene carrier status • MCI due to AD • Mild dementia due to AD	Subgroup analyses were provided in Appendix E of the CS and scenario analyses for MCI due to AD and mild dementia due to AD are presented.	N/A – in line with the NICE final scope.	N/A – in line with the NICE final scope.
Special considerations including issues related to equity or equality	None specified.	None identified.	N/A – in line with the NICE final scope.	N/A – in line with the NICE final scope.
Based on Table 1 and pages 10 to 12 of the CS[2]				

	Final scope issued by NICE	Decision problem addressed in the CS	Rationale if different from the final NICE scope	EAG Comment
AChEi = acetylcholinesterase inhibitor; AD = Alzheimer's disease; *ApoE4* = apolipoprotein E4; CS = company submission; EAG = Evidence Assessment Group; HRQoL = health-related quality of life; MCI = mild cognitive impairment; N/A = not applicable; NICE = National Institute of Health and Care Excellence; UK = United Kingdom				

2.1 Population

The population defined in the National Institute for Health and Care Excellence (NICE) final scope[3]is: People with mild cognitive impairment (MCI) or mild dementia due to Alzheimer's disease (AD).The population in the decision problem of the company submission (CS) is consistent with the scope.[2, 3] However, the actual population in the key clinical trial, Clarity AD, and of those eligible for lecanemab is narrower, being defined by the presence of amyloid beta (Aβ) pathology:

"The presence of Aβ pathology must be confirmed via an appropriate test prior to initiating treatment. It is anticipated that the test to confirm brain Aβ pathology will be carried out using one of the following:

- *Cerebrospinal fluid (CSF) biomarker test*
- *Amyloid positron emission tomography (PET) scan"* (p. 14, CS)[2]

As stated in the CS, this testing is not routinely used in the National Health Service (NHS) to diagnose AD.[2] Therefore, there are consequences of this testing that need to be valued to assess the effectiveness and cost effectiveness of lecanemab.[4] These include the cost of testing and any potential harms to health of those tested, who include more patients than those who turn out to be eligible for lecanemab. Indeed, the potential harm of lumbar puncture (for the CSF biomarker test) and PET scan are recognised in the NICE guideline:[5]

"The committee discussed the potentially stressful and unpleasant diagnostic tests that could be used in a specialist setting. These include lumbar puncture to obtain cerebrospinal fluid (CSF) for biomarker tests, MRI and other imaging tests. These tests may not be well tolerated by all patients, particularly those with claustrophobia (MRI) or people with more severe dementia. The committee noted that it was important to use these tests only if they are required to reduce diagnostic uncertainty, if the person with suspected dementia/with dementia requiring subtype diagnosis agrees and if they can comply with test requirements. The committee agreed that to avoid unnecessary tests being undertaken, it was important to include a specific recommendation stating these tests only be undertaken if they would reduce diagnostic uncertainty and reducing that uncertainty would change management."

The CS (Appendix E) also includes subgroup analyses, as specified in the NICE scope,[3] by apolipoprotein E4 (*ApoE4*) genotype and by baseline disease stage (MCI due to AD and mild dementia due to AD).[2]

Participants in the Clarity AD trial were required to have a diagnosis of early AD defined by:

- Meeting the National Institute on Aging and Alzheimer's Association (NIA-AA) core clinical criteria for MCI due to AD–intermediate likelihood, or for probable AD dementia, respectively, and
- Having a global Clinical Dementia Rating (CDR) score of 0.5 (for MCI due to AD) or 0.5-1 (for mild AD dementia), and
- Having a CDR Memory Box score of 0.5 or greater at screening and baseline

and to have a positive biomarker for brain amyloid pathology (CS, Table 8, page 44-48).[2]

The draft summary of product characteristics (SmPC) from the Medicines and Healthcare products Regulatory Agency (MRHA)[6] includes the following in relation to risk factors (other than concomitant medication) for intracerebral haemorrhage:

[redacted]

EAG comment: It should be noted that both Clarity AD[7] and Study 201[8] excluded people: [redacted] These exclusion criteria means that no safety or efficacy data are available for patients with these risk factors. No information was provided about the numbers of patients excluded, from either study, based on these criteria.

2.2 Intervention

The NICE final scope specifies the intervention as lecanemab plus established clinical management,[3] and both the CS and the Clarity AD study evaluated lecanemab 10 mg/kg, biweekly intravenous (IV), as an add-on treatment to patients' usual care, which is in-line the proposed license indication. The NICE final scope defines established clinical management without lecanemab including, but not limited to:

- For MCI due to AD, non-pharmacological management
- For mild dementia due to AD, an acetylcholinesterase inhibitor (AChEi) plus non-pharmacological management.

NICE guidance, 'Dementia: assessment, management and support for people living with dementia and their carers' (NG97), currently recommends three AChEis, donepezil, galantamine and rivastigmine as monotherapy options for managing mild to moderate AD, and memantine for managing moderate AD where there is intolerance of, or a contraindication to, AChEi or severe AD.[5]

In the lecanemab arm of the Clarity AD trial, [redacted] participants were reported to be taking at least one concomitant AD medication, [redacted] participants were reported to be taking donepezil, [redacted] participants were reported to be taking galantamine, [redacted] participants were reported to be taking rivastigmine, [redacted] participants were reported to be taking memantine, and [redacted] participants were reported to be taking donepezil plus memantine (CS, Appendix O).[9] Additional data on concomitant use of symptomatic AD medications, stratified by disease stage (MCI due to AD and mild dementia due to AD) were provided by the company in their clarification response (see Table 3.5).[10]

The CS (Section B.2.12.2.1 Strengths of the evidence base) states that: *"In both arms of Clarity AD, approximately half of patients were already receiving AD medication. In Europe, approximately 31% of MCI patients receive AChEis and 8% receive memantine (both off-label since no treatments are recommended for MCI), and up to 89% of mild AD patients receive AChEis and 7-21% receive memantine,"*[2] citing a 2023 systematic review;[11] this systematic review did not include any data, from UK only studies, on symptomatic treatment for people with MCI due to AD and included only one UK study of people with mild dementia due to AD (n=201) which reported that 82.6% were taking an AChEi monotherapy and 1% were taking memantine monotherapy. The EAG sought the opinion of a clinical expert regarding the UK use of AChEi and memantine, in people with MCI due to AD and people with mild dementia due to AD. The clinical expert noted that:[12] *"Prescribing practice in UK is not typical of many other countries around the world (for example, prescribing for MCI is common in US, but not UK),"* and provided the following responses about the use of specific symptomatic treatments:

- *"I do not know of any reliable current UK data, but my strong impression is that a minority of UK patients with MCI due to AD receive an AChEi and almost none receive memantine."*
- *"I do not know of reliable UK data, but I think most people with mild AD dementia will be offered treatment and about 70% will subsequently take an AChEi and about 5% will take memantine."*

2.3 Comparators

The NICE final scope[3] defines the comparator(s) as established clinical management without lecanemab including, but not limited to:

- For MCI due to AD, non-pharmacological management
- For mild dementia due to AD, an AChEi plus non-pharmacological management.

The company amended the comparator for mild dementia to *"AChEi and/or non-pharmacological management,"* i.e. including the possibility of no AChEi in the decision problem. In the comparator arm of the Clarity AD trial, [redacted] participants were reported to be taking at least one concomitant AD medication, [redacted] participants were reported to be taking donepezil, [redacted] participants were reported to be taking galantamine, [redacted] participants were reported to be taking rivastigmine, [redacted] participants were reported to be taking memantine, and [redacted] participants were reported to be taking donepezil plus memantine (CS, Appendix O).[9] Additional data on concomitant use of symptomatic AD medications, stratified by disease stage (MCI due to AD and mild dementia due to AD) were provided by the company in their clarification response (see Table 3.5).[10]

Please see Section 2.2 Interventions for discussion of UK guidance and current practice with respect to the use of symptomatic treatments in people with mild AD.

EAG comment: The EAG considers that it is not clear that the concomitant treatments, used in both the lecanemab and placebo arms of the Clarity AD trial (the key source of clinical effectiveness estimates for the CS), were consistent with established clinical management in the UK.

At clarification,[13] the EAG requested subgroup analyses, for all reported outcomes (Clinical Dementia Rating scale – Sum of Boxes [CDR-SB], Alzheimer's Disease Assessment Scale-Cognitive subscale [ADAS-Cog14], Alzheimer's disease composite score [ADCOMS] and Alzheimer's Disease

Cooperative Study-Activities of Daily Living Scale for use in Mild Cognitive Impairment [ADCS ADL-MCI]), for:

- Participants with MCI due to AD who did not receive symptomatic AD medication (AChEi or memantine) during the Clarity AD study (consistent with the final scope and close to clinical expert opinion (see Section 2.2)
- Participants in the Clarity AD study with mild dementia due to AD, excluding:
    a) Those participants who received memantine during the study (consistent with the company's definition of the decision problem)
    b) Those patients who received memantine during the study and those patients who did not receive AChEi during the study (consistent with the final scope).

Note that clinical expert opinion is that subgroup (b) is probably the most common, but that a sizeable minority of mild dementia patients might not currently be taking any medication. It should also be noted that the percentage of those patients with mild AD in the Clarity AD who received AChEi was not much less than 70% ([redacted] in the lecanemab and [redacted] in the placebo arm,[10]).

Subgroup analyses were provided in the company's response to clarification (see Section 3.2.6.1).[10]

2.4 Outcomes

The NICE final scope lists the following outcome measures:[3]

- Cognitive and functional impairment
- Non-cognitive symptoms (e.g., behavioural and psychiatric symptoms)
- Mortality
- Ability to remain independent
- Admission to full-time care
- Health-related quality of life (HRQoL)
- Adverse effects of treatment

The Clarity AD trial reported measures of cognitive and functional impairment (CDR-SB, ADAS-Cog14, ADCOMS and ADCS-ADL-MCI), HRQoL (European Quality of Life-5 Dimensions, EQ-5D) and AE.[2, 7] Although the outcome measures used include aspects of function/activities of daily living (ADL), ability to remain independent was not explicitly assessed/reported. Admission to full-time care was not an outcome measure in the Clarity AD study; given that study participants had early AD at baseline, the 18-month duration of the core study would be unlikely to be sufficient for adequate assessment of this outcome. The CS did not include any information about the effect of lecanemab on behavioural or psychiatric symptoms of AD.

EAG comment: The EAG considers that, given the nature of the condition and of the intervention (lecanemab is a disease-modifying treatment, rather than a treatment of symptoms), 18-months follow-up is unlikely to be sufficient to adequately assess the reported treatment effects, e.g., any observed initial delay in disease progression may not extrapolate to long-term benefit if the delay in progression does not remain constant and persist beyond 18 months, or to assess key clinical outcomes such as progression to moderate/severe AD or admission to full-time care.

At clarification,[13] the EAG requested provision of results from early data cuts from the open-label extension (OLE) of Clarity AD or confirmation that no data are yet available from the OLE. Early results from the OLE, provided in the company's clarification response,[10] are included in Section 3.2.5.

The EAG also requested confirmation that there are no data available to inform the effects of lecanemab on the outcomes *"non-cognitive symptoms (behavioural and psychiatric"* or *"admission to full-time care."* The company confirmed that data on admission to full-time care were not collected in Clarity AD and noted that: *"Data on patient anxiety/depression is available from Clarity AD, as part of the EQ-5D-5L domains. Additionally, data on patient mood is available as part of the QOL-AD domains."*[10]

2.5 Other relevant factors

Lecanemab is the first treatment that targets the underlying pathophysiology of AD to receive regulatory approval for early AD in United States of America (USA) and Japan.[2]

According to the company (CS, Section B.2.12.3):[2] *"Clarity AD demonstrates that treatment with lecanemab leads to statistically significant and clinically meaningful reductions in decline in clinical measures of cognition and function compared to placebo at 18 months."* and *"Patient and care partner output from Clarity AD show that the benefits offered by lecanemab are clinically meaningful."* The company further state that: *"Considering the extreme unmet need in AD, owing to the low quality of life of patients and the lack of a disease-modifying treatment (DMT) at any stage of disease, lecanemab would provide hope for early AD patients who face a journey through progressive disease."*

According to the company: *"There are no known equality issues relating to the use of lecanemab in patients with early AD."* (CS, Section B.1.4).[2]

3. CLINICAL EFFECTIVENESS

3.1 Critique of the methods of review(s)

A systematic literature review (SLR) was carried out in 2023, according to NICE requirements, to identify the available evidence on the efficacy and safety of existing pharmacological and non-pharmacological treatments for early AD (MCI due to AD and mild dementia due to AD); details are provided in Appendix D of the CS.[9] In addition to the clinical SLR, a second SLR was carried out to identify relevant data on the natural history of patients with MCI due to AD and mild dementia due to AD.[9]

3.1.1 Searches

The following paragraphs contain summaries and critiques of the searches related to clinical effectiveness presented in the CS.[2] The Canadian Agency for Drugs and Technologies in Health (CADTH) evidence-based checklist for the Peer Review of Electronic Search Strategies (PRESS), was used to inform this critique.[14, 15] The EAG has presented only the major limitations of each search strategy in the report.

A summary of the sources searched is provided in Table 3.1.

Table 3.1: Data sources for Appendix D: Identification, selection and synthesis of clinical evidence (as reported in CS)

Resource	Host/Source	Date Ranges	Date searched
Electronic databases			
Embase	Embase.com	Inception-2023/08/31	31.8.23
MEDLINE	Embase.com	Inception-2023/08/31	31.8.23
MEDLINE In-Process	PubMed	Inception-2023/08/31	31.8.23
CENTRAL	Wiley	Inception-2023/08/31	31.8.23
CDSR	Wiley	Inception-2023/08/31	31.8.23
Conferences			
AAIC	2020-23: Internet	2020-2023	Conference searches conducted between 16-20 Oct 2023
EAN	2020: Embase.com 2021-23: Internet	2020-2023	
ANA	2020-23: Annals of Neurology (Wiley)	2020-2023	
AAN	2020-23: Embase.com	2020-2023	
ADI	2020 & 2022 (biennial): Internet	2020-2023	
CTAD	2020-22 (2023 NYP): Internet	2020-2023	
ISPOR	2020-23: Internet	2020-2023	
AD/PD	2021-23: Internet	2020-2023	

Resource	Host/Source	Date Ranges	Date searched
	(2020 not available)		
AAIC = Alzheimer's Association International Conference; AD = Alzheimer's disease; ANA = American Neurological Association; AAN = American Academy of Neurology; ADI = International Conference of Alzheimer's Disease International; CS = company submission; CDSR = Cochrane Database of Systematic Reviews; CENTRAL = Cochrane Central Register of Controlled Trials; CTAD = Clinical Trials on Alzheimer's Disease; EAN = Annual Congress of the European Academy of Neurology; ISPOR = International Society for Pharmacoeconomics and Outcomes Research; NYP = not yet published; PD = Parkinson's disease			

EAG comment: Searches were undertaken in August 2023 to identify relevant clinical evidence for adult patients with early AD. The CS, Appendix D and the company's response to clarification provided sufficient details (including database host(s), date searched, and date ranges covered) for the EAG to appraise the literature searches.[2, 9, 10]

A good range of databases and conference proceedings were searched.

The company reported that searches utilised study design filters based on validated filters from the Scottish Intercollegiate Guideline Network (SIGN) and CADTH.

The EAG was concerned that the MEDLINE and Embase search conducted via Embase.com contained a limit to English language which may have introduced potential language bias. Current best practice states that "Whenever possible review authors should attempt to identify and assess for eligibility all possibly relevant reports of trials irrespective of language of publication".[16] However this was not included in either the Cochrane or PubMed searches, which may have helped to mitigate against some loss of recall.

The EAG asked the company to clarify whether the reported MEDLINE/Embase search conducted via Embase.com was a single search conducted simultaneously over both the Embase and MEDLINE individual databases, or a single search of Embase conducted on the understanding that it now contains all records from MEDLINE. The company responded that "*Yes, a single search was conducted to cover both Medline and Embase searches via the Embase.com interface due to overlapping coverage between the two databases. However, PubMed was also searched separately to identify any in-process or Ahead of Print citations*".[10] The EAG took this as confirmation that a simultaneous search of the two databases had taken place. This approach has limitations when using subject heading terms. It appeared that only Embase subject heading terms (Emtree) were used in the search strategy. Although simultaneous searching of Embase.com should automatically identify and search for equivalent MEDLINE subject heading terms (MeSH), as the EAG did not have access to Embase.com for testing it was unclear if this was the case for all potentially useful MeSH terms. Given the potential limitations of this approach, the EAG considered it preferable to search each database separately, or at least to ensure inclusion of both Emtree and MeSH terms in the search strategy.

The EAG noted that a randomised controlled trial (RCT) filter was included in the Cochrane Library search. As both the Cochrane Database of Systematic Reviews (CDSR) and the Cochrane Central Register of Controlled Trials (CENTRAL) are pre-filtered resources, this is not appropriate and may result in unnecessarily restricting the results retrieved. Further to this an additional limit to exclude MEDLINE and Embase records was also applied. Whilst this might appear justifiable given that these resources have been searched separately, it removes the opportunity for relevant items not retrieved by the Embase strategy to be picked up by via an alternative resource, especially given the single search of MEDLINE/Embase as described above. The EAG thinks it preferable to run full searches across all databases and deduplicate results once all of the searches have been run. This approach ensures that

duplicate references are removed and unique references retrieved by another resource due to differences in indexing or search interface are not missed. Without rerunning the searches, it is unclear if this approach may have adversely affected the overall recall of results.

Separate searches to retrieve information regarding adverse events (AEs) for safety outcomes for lecanemab were not conducted. In their response to clarification the company cited the searches undertaken to inform clinical effectiveness and confirmed "*No additional searches were conducted to identify AEs for lecanemab or any other treatment of interest, as these were sourced from Clarity AD, the pivotal study supporting the marketing authorisation of lecanemab.*"[10] However, given the searches reported in Appendix D section D.1 were limited to RCTs, guidance by the Centre for Reviews and Dissemination (CRD)[17]and Golder et al[18] recommend that if searches have been limited by a study design filter, additional searches should be undertaken to ensure that AEs that are long-term, rare or unanticipated are not missed.

3.1.1.1 Identification, selection and synthesis of natural history of AD data

The company reported that the primary objective of these additional searches was to identify and summarise the evidence describing the probability of natural disease progression from MCI into AD.

Table 3.2: Data sources for Appendix D: Identification, selection and synthesis of clinical evidence natural history of AD data (as reported in CS)

Resource	Host/Source	Date Ranges	Date last searched
Electronic databases			
Embase	Embase.com	Inception-2023/08/31	SLR4: 31.8.2023
MEDLINE	Embase.com	Inception-2023/08/31	SLR4: 31.8.2023
MEDLINE In-Process	PubMed	Inception-2023/08/31	SLR4: 31.8.2023
CENTRAL	Wiley	Inception-2023/08/31	SLR4: 31.8.2023
CDSR	Wiley	Inception-2023/08/31	SLR4: 31.8.2023
Conferences			
AAIC	2020-23: Internet	2020-2023	Conference searches conducted between 16-20 Oct 2023
EAN	2020: Embase.com 2021-23: Internet	2020-2023	
ANA	2020-23: Annals of Neurology (Wiley)	2020-2023	
AAN	2020-23: Embase.com	2020-2023	
ADI	2020 & 2022 (biennial): Internet	2020-2023	
CTAD	2020-22 (2023 NYP): Internet	2020-2023	
ISPOR	2020-23: Internet	2020-2023	
AD/PD	2021-23: Internet (2020 not available)	2020-2023	

Resource	Host/Source	Date Ranges	Date last searched
AAIC = Alzheimer's Association International Conference; AAN = American Academy of Neurology; AD = Alzheimer's disease; ADI = International Conference of Alzheimer's Disease International; ANA = American Neurological Association; CDSR = Cochrane Database of Systematic Reviews; CENTRAL = Cochrane Central Register of Controlled Trials; CS = company submission; CTAD = Clinical Trials on Alzheimer's Disease; EAN = Annual Congress of the European Academy of Neurology; ISPOR = International Society for Pharmacoeconomics and Outcomes Research; NYP = not yet published; PD = Parkinson's disease; SLR = systematic literature review			

EAG comment: The company provided a timeline of the four searches undertaken and the search strategies used. The original search was run in Nov 2018 and updated in February 2020, June 2021 and August 2023. Strategies were reported in a single table for each resource with the results of the different iterations reported in the final lines (please see below for example from Table 22, appendix D).[9] It would have been preferable for the database search strategies to be presented exactly as run, rather than copied into a tabular format, as item 8 of the Preferred reporting items for systematic reviews and meta-analyses (PRISMA-S) checklist recommends.[19] The Cochrane Handbook also recommends that *"...bibliographic database search strategies should be copied and pasted into an appendix exactly as run and in full, together with the search set numbers and the total number of records retrieved by each search strategy. The search strategies should not be re-typed, because this can introduce errors".*[20] However, given the number of update searches performed the EAG understands the rationale for this approach. Working on the understanding that all iterations of a search utilised the same strategy as reported in the provided table, apart from where clear deviations were described as in the point below, strategies appeared well structured and reproducible.

23	#18 AND #22	625
24	#18 AND [english]/lim AND [1-1-1966]/sd NOT [1-11-2018]/sd	1,567
25	#23 AND [english]/lim AND [1-11-2018]/sd NOT [1-2-2020]/sd	98
26	#23 AND [english]/lim AND [1-2-2020]/sd NOT [27-6-2021]/sd	60
27	#23 AND [english]/lim AND [27-6-2021]/sd NOT [31-8-2023]/sd	136
28	#24 OR #25 OR #26 OR #27	1,861

The company reported that the four searches were conducted iteratively across various timeframes. The EAG noted that update searches carried an additional facet making them more focused:

Search 1: Disease progression + (AD or dementia or cognitive impairment)

Searches 2-4: Disease progression + (AD or dementia or cognitive impairment) + dementia test/rating scales.

Searches were conducted across a good range of databases and the company confirmed at clarification that *"The same keywords were searched in all conference proceedings for all SLRs."*[10]

The EAG noted that a single search conducted to cover both MEDLINE and Embase searches via the Embase.com platform was used as described in the clinical effectiveness searches, therefore the same limitations will have applied.

3.1.2 Inclusion criteria

The eligibility criteria used in the search strategy for RCTs and non-RCTs is presented in Table 3.3.

Table 3.3: Eligibility criteria used in the SLR of clinical effectiveness evidence

	Inclusion	Exclusion	Company's Rationale
Population	Patients (≥18 years, any race or gender) with MCI due to AD Patients (≥18 years, any race or gender) with mild dementia due to AD Patients (≥18 years, any race or gender) with MCI due to AD and mild dementia due to AD (both patient cohorts included) Studies of patients with MCI due to unknown reasons were eligible for inclusion only if mild dementia due to AD is also presented in the study (rationale - this indicates AD could have been included among the unknown reasons for MCI)	Patients with MCI due to unknown reasons Patients with MCI due to non-AD (not unknown) reasons Patients with moderate dementia due to AD Patients with severe dementia due to AD Patients with severity not reported Patients with pre-clinical AD Patients with a specific type of dementia other than AD, e.g., Parkinson's, vascular dementia, or frontotemporal dementia	AD categories included and excluded according to the NICE scope
Interventions	Lecanemab Donepezil Rivastigmine Galantamine	N/A	Recommended as monotherapy options by NICE for managing mild-to-moderate dementia due to AD.[5]
	Memantine (only to be considered when studies evaluating memantine also evaluate any AChEi or listed non-pharmacological therapy)	Studies evaluating memantine alone	Recommended as a monotherapy option for managing AD for people with 1) moderate dementia due to AD who are intolerant of or have a contraindication to AChEi and 2) severe dementia due to AD.[5]
	Group cognitive stimulation therapy to people living with mild to moderate dementia due to AD Group reminiscence therapy for people living with mild to moderate dementia due to AD	Other non-pharmacological interventions (that are not recommended), e.g., acupuncture, vitamin E supplements, ginseng, herbal formulations, interpersonal therapy, magnetic stimulation	Non-pharmacological agents with the final recommendations made in NICE Guideline 97.[5]

	Inclusion	Exclusion	Company's Rationale
	Cognitive rehabilitation or occupational therapy to support functional ability in people living with mild to moderate dementia due to AD		
Comparators	Placebo/best supportive care Active symptomatic treatments, i.e., donepezil, rivastigmine, galantamine, and memantine Non-pharmacological treatments, i.e., cognitive stimulation therapy, reminiscence therapy, cognitive rehabilitation, and occupational therapy Studies should evaluate relevant treatments in all the randomised arms of interest	N/A	N/A
Outcomes	ADCOMS CDR global score CDR-SB MMSE score ADAS-Cog ADAS-Cog MCI ADCS-ADL ADCS-ADL-MCI score Amyloid-beta PET SUVR AEs, i.e., overall, serious/severe (grade 3+), treatment-related, treatment-related serious/severe (grade 3+) Specific AEs: ARIA-E, ARIA-H, headache, fall, diarrhoea, dizziness, infusion-related reactions, and skin rash	Studies not reporting relevant outcomes of interest were excluded	N/A

	Inclusion	Exclusion	Company's Rationale
	Study withdrawals and treatment discontinuations		
Study design	RCTs only Relevant trials should have a comparison of the above-listed set of interventions and comparators (i.e., both the treatment arms should be of relevance)	RCTs with only one treatment arm of interest Non-RCTs Observational (retrospective, prospective) studies Database/registry-based studies Case-control Single-arm trials Case reports, case series	It is aligned with the study design of trials evaluating lecanemab RCTs are classified as the gold standard of evidence
Timeframe	Database inception to August 31, 2023	N/A	To retrieve comprehensive evidence to support the review objectives
Country	No restriction	N/A	
Language	Studies with full texts published in the English language only	Studies with full texts published in non-English language	N/A
Publication type	Peer-reviewed journal articles and conference abstracts (searched for the previous four years, 2020-2023)	Editorials, newspaper articles, book sections, expert opinion or commentary, trial protocols, and reviews	N/A
Additional parameters (1)	N/A	RCTs published as conference abstracts (only) before 2020	Less likely to be published as a complete manuscript journal publication after a gap of 4-5 years
Additional parameters (2)	N/A	RCTs evaluating relevant treatments (listed above) in an add-on/background/concomitant manner	Such treatment combinations are not of interest as the primary set of randomised treatments are non-relevant

Adapted from Table 11 of the CS, Appendix D[9]

AChEi = acetylcholinesterase inhibitor; AD = Alzheimer's disease; AE = adverse events; ADAS-Cog MCI = Alzheimer's Disease Assessment Scale-Cognitive-Mild Cognitive Impairment; ADAS-cog = Alzheimer's Disease Assessment Scale-Cognitive; ADCOMS = Alzheimer's disease composite score; ADCS-ADL = Alzheimer's Disease Cooperative Study-Activities of Daily Living; ADCS-ADL-MCI = Alzheimer's Disease Cooperative Study-Activities of Daily Living-Mild Cognitive Impairment; ARIA-E = amyloid-related imaging abnormality-oedema/effusion; ARIA-H = amyloid-related imaging abnormality-microhaemorrhage and haemosiderin deposit; CDR global score = Clinical Dementia Rating scale global score; CDR-SB = Clinical Dementia Rating - Sum of Boxes; CS = company submission; MCI = mild cognitive impairment; MMSE = Mini-Mental State Examination; NICE = National Institute for Health and Care Excellence; PET = positron emission tomography; RCT = randomised controlled trial; SLR = systematic literature review; SUVR = standardised uptake value ratio

3.1.3 Critique of data extraction

For the clinical SLR, a PRISMA flow chart was provided (CS Appendix D, Figure 6) and included studies were summarised in tables and text (CS Appendix D, Section 1.5).[9] All stages of study selection and data extraction were undertaken by two reviewers, independently; any disagreements were resolved by a third reviewer (CS Appendix D, Section 1.5).[9] A similar process was followed for the natural history SLR (CS Appendix D, Section 2.3).[9]

EAG comment: The EAG considers that, for both SLRs, the study selection and data extraction processes were appropriate and followed accepted methods to minimise the potential for error and bias.

3.1.4 Quality assessment

A risk of bias assessment was completed, using the Cochrane risk of bias tool 2.0,[21] for each of the 16 RCTs identified by the SLR. Risk of bias assessments were completed by two reviewers, independently, with any disagreements resolved by a third reviewer (CS Appendix D, Section 1.5).[9] The results of the risk of bias assessments are summarised in text and tables (CS Appendix D, Section 1.5.3 and Table 20,[9] and CS, Section B.2.5 and Table 15[2]).

EAG comment: The EAG considers that, for the clinical SLR, risk of bias assessment was undertaken using an appropriate tool and that accepted methods to minimise the potential for error and bias were followed. No risk of bias assessment was reported for studies included in the natural history SLR.

3.1.5 Evidence synthesis

The 16 RCTs included in the clinical SLR are summarised in tables and text (CS Appendix D, Section 1.5). Details of the 40 studies included in the natural history SLR are provided (CS Appendix D, Tables 26-28), and results are summarised for the four studies that reported conversion or transition probabilities across all stages of AD (CS Appendix D, Section 2.6.2).[9]

3.2 Critique of trials of the technology of interest, their analysis and interpretation (and any standard meta-analyses of these)

The CS identified two placebo-controlled RCTs of lecanemab, Clarity AD and Study 201 (Table 3.4).[2]

The clinical effectiveness section of the CS did not include any results for Study 201 and did not include results for the outcome Columbia Suicide Severity Rating Scale (C-SSRS).[2]

EAG comment: At clarification,[13] the EAG requested provision of results for all reported outcomes (CDR-SB, ADAS-Cog14, ADCOMS, Mini-mental state examination [MMSE] and Functional Assessment Questionnaire [FAQ]), for patients in Study 201 who were treated with 10 mg/kg biweekly lecanemab. Results provided for Study 201,[10] are summarised in Section 3.2.7.

The EAG also requested provision of any available data for *"non-cognitive symptoms (behavioural and psychiatric"* or *"admission to full-time care".* The company confirmed that data on admission to full-time care were not collected in Clarity AD and noted that: *"Data on patient anxiety/depression is available from Clarity AD, as part of the EQ-5D-5L domains. Additionally, data on patient mood is available as part of the QOL-AD domains."*[10]

3.2.1 Design of Clarity AD

Clarity AD is an international, multi-centre, randomised, double-blind, parallel-group, placebo-controlled clinical trial to evaluate the safety and efficacy of lecanemab (10 mg/kg biweekly IV infusion) in patients with early AD with confirmed amyloid pathology indicated by positive amyloid load.[2] The methodology of Clarity AD is summarised in Table 3.5.[2]

Clarity AD was conducted across 14 countries including eight sites in the UK and consisted of:

- A completed pre-randomisation phase (screening period and baseline period, up to 150 days)
- A completed 18-month core study (randomisation phase)
- An ongoing OLE (CS, Section B.2.11).

Figure 3.1 shows participant flow in Clarity AD.[2]

EAG comment: At clarification,[13] the EAG requested confirmation that, as indicated in the clinical study report (CSR),[7] Clarity AD included [redacted] UK participants; this was confirmed by the company,[10] who further noted that there were [redacted] UK patients in each of the MCI due to AD and mild dementia due to AD subgroups. In addition, the CS indicates that approximately [redacted]% of participants in the Clarity AD study had MCI at baseline and approximately [redacted]% had mild AD.[2] By contrast, clinical expert opinion (sought by the EAG) has indicated that; *"In the UK, patients are currently more likely to present at the mild dementia than MCI stage, and so the proportions offered lecanemab might be reversed (i.e. [redacted]% MCI, [redacted]% dementia)."*

The CS (Section B.2.3.1) notes that: *"Any patient who completed 18 months treatment in the core study (Visit 42 [Week 79]) had the option to continue into the OLE if inclusion and exclusion criteria were met. All patients in the OLE receive open-label lecanemab 10 mg/kg biweekly for up to 48 months (4 years), until the drug is commercially available in the country where the patient resides, or until the benefit-to-risk assessment from treatment with lecanemab is no longer considered favourable, whichever comes first. Of the 729 lecanemab and 757 placebo patients that completed the Clarity AD core study, 671 lecanemab and 714 placebo patients entered the OLE; whilst 58 lecanemab and 43 placebo patients did not enter the OLE upon completion of the core study. Of those who completed the core study, 43 lecanemab patients and 60 placebo patients has progressed to moderate or severe AD, therefore did not meet the eligibility criteria for inclusion in the OLE."*[2]

EAG comment: The in-text reporting of numbers of participants completing Clarity AD and entering the OLE appears to be inconsistent with the information provided in the study flow chart (Figure 3.1).

Table 3.4: Clinical effectiveness evidence for lecanemab (Clarity AD and Study 201)

Study	Clarity AD (BAN2401-G000-301) (NCT03887455)	Study 201 (BAN2401-G000-201) (NCT01767311)
Study design	Phase III, multicentre, randomised, placebo-controlled, double-blind, parallel-group, 18-month clinical trial	Phase II, multicentre, randomised, placebo-controlled, double-blind, parallel-group, 18-month clinical trial
Population	Adult patients with early AD	Adult patients with early AD
Intervention(s)	Lecanemab 10 mg/kg biweekly administered as IV infusion	Lecanemab administered as IV infusion via one of the following dosing schedules (in addition to symptomatic treatment): 2.5, 5, or 10 mg/kg bi-weekly or 5 or 10 mg/kg monthly
Comparator(s)	Placebo: biweekly administered as IV infusion (in addition to symptomatic treatment)	Placebo: biweekly administered as IV infusion (in addition to symptomatic treatment)
Reported outcomes specified in the NICE final scope and decision problem	Cognitive and functional impairment: CDR-SB, Global CDR, ADCOMS, Modified iARDS Cognitive impairment: ADAS-Cog14 Functional impairment: ADCS-ADL-MCI Non-cognitive symptoms (e.g., behavioural symptoms): C-SSRS Mortality Adverse effects of treatment Patient and carer HRQoL; EQ-5D-5L (patient-reported, partner as a proxy, study partner), QOL-AD (patient-reported, partner as a proxy), ZBI (study partner only)	Cognitive and functional impairment: ADCOMS, CDR-SB Cognitive impairment: ADAS-Cog14, MMSE Functional impairment: FAQ Mortality Adverse effects of treatment
Subgroup analyses specified in the NICE final scope and decision problem	*ApoE4* gene carrier status Mild cognitive impairment due to AD Mild dementia due to AD	Unclear

Based on Table 6 of the CS[2]

AD = Alzheimer's disease; ADAS-Cog14 = Alzheimer's Disease Assessment Scale-Cognitive subscale; ADCOMS = Alzheimer's disease composite score; ADCS-ADL-MCI = Alzheimer's Disease Cooperative Study – Activities of Daily Living for Mild Cognitive Impairment; *ApoE4* – apolipoprotein E4; CDR = Clinical Dementia Rating; CDR-SB = Clinical Dementia Rating scale – Sum of Boxes; C-SSRS = Columbia Suicide Severity Rating Scale; EQ-5D = European Quality of Life-5 Dimensions; HRQoL = health-related quality of life; iARDS = Integrated Alzheimer's disease rating scale; IV = intravenous; MCI = mild cognitive impairment; MMSE = mini-mental state examination; QOL-AD = Quality of life in Alzheimer's disease; ZBI = Zarit's Burden Interview

Table 3.5: Clarity AD methodology

Study	Clarity AD (NCT03887455)
Study design and objective	To evaluate the efficacy of lecanemab in participants with early AD by determining the superiority of lecanemab compared with placebo on the change from baseline in the CDR-SB at 18 months of treatment in the core study, with sample size calculations driven by Study 201. Based on data from Study 201, an estimated standard deviation of the change from baseline CDR-SB at 18 months in placebo was 2.031 and an estimated treatment difference was 0.373 in all patients. Therefore, assuming an estimated 20% dropout rate at 18 months in Clarity AD, a total sample size of 1,566 patients had 90% power to detect the treatment difference. Lecanemab 10 mg/kg biweekly was identified as the most efficacious dose regimen based on ADCOMS in the dose-finding Study 201 and therefore was used in Clarity AD. This study also evaluated the long-term safety and tolerability of lecanemab in participants with early AD in the OLE and whether the long-term benefits of lecanemab at the end of the core study were maintained over the OLE.
Study location	235 sites in: North America (112), Europe (including Australia) (55), Asia-Pacific (47), and China (21) Of the 55 sites in Europe, eight sites were in UK.
Method of randomisation	Patients were assigned to treatments, (allocated 1:1; lecanemab:placebo), based on a computer-generated randomisation scheme that was reviewed and approved by an independent statistician. Patients were stratified according to clinical subgroup; presence or absence of ongoing approved AD treatment (e.g., AChEis, memantine, or both); *ApoE4* status (i.e., *ApoE4* carrier or noncarrier); and geographical region.
Eligibility criteria for participants	Diagnosis of early AD dementia, defined by: Meeting the NIA-AA core clinical criteria for MCI due to AD–intermediate likelihood, or for probable AD dementia, respectively,[22] and Having a global CDR score of 0.5 (for MCI due to AD) or 0.5-1 (for mild AD dementia), and Having a CDR Memory Box score of 0.5 or greater at screening and baseline Key inclusion criteria Objective impairment in episodic memory as indicated by at least one standard deviation below age adjusted mean in the WMS-IV LMII[23] Male and female patients 50 to 90 years, inclusive MMSE score ≥22 & ≤30 at screening and baseline Positive biomarker for brain amyloid pathology BMI greater than 17 and less than 35 at screening If patients were receiving an approved AD treatment, such as AChEis, memantine, or both, they had to have been on a stable dose for at least 12 weeks prior to baseline

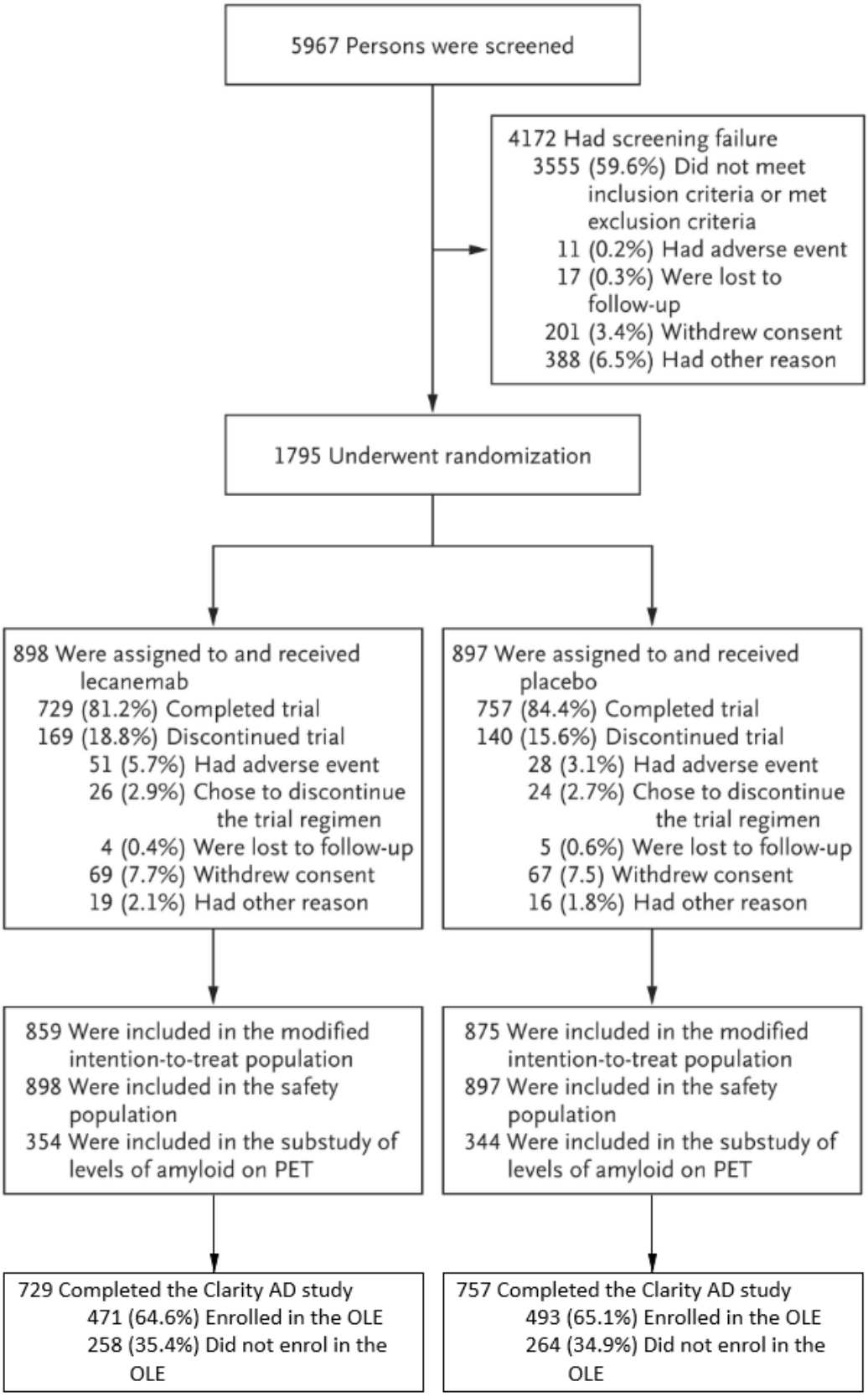
	Have an identified study partner, defined as a person able to support the patient for the duration of the study and who spends at least eight hours per week with the patient Provided written informed consent Willing and able to comply with all aspects of the protocol Key exclusion criteria Any neurological condition that could be contributing to cognitive impairment above and beyond that caused by the patient's AD. History of TIAs, stroke, or seizures within 12 months of screening. Any psychiatric diagnosis or symptoms, (e.g., hallucinations, major depression, or delusions) that could interfere with study procedures in the patient. GDS score greater than or equal to eight at screening. Contraindications to MRI scanning, including cardiac pacemaker/defibrillator, ferromagnetic metal implants (e.g., in skull and cardiac devices other than those approved as safe for use in MRI scanners). Evidence of other clinically significant lesions on brain MRI at screening that could indicate a dementia diagnosis other than AD. Other significant pathological findings on brain MRI at screening, including but not limited to: more than four microhaemorrhages (defined as 10 mm or less at the greatest diameter); a single macrohaemorrhage greater than 10 mm at greatest diameter; an area of superficial siderosis; evidence of vasogenic oedema; evidence of cerebral contusion, encephalomalacia, aneurysms, vascular malformations, or infective lesions; evidence of multiple lacunar infarcts or stroke involving a major vascular territory, severe small vessel, or white matter disease; space occupying lesions; or brain tumours. Hypersensitivity to lecanemab or any of the excipients, or to any monoclonal antibody treatment. Any immunological disease which was not adequately controlled, or which required treatment with immunoglobulins, systemic monoclonal antibodies (or derivatives of monoclonal antibodies), systemic immunosuppressants, or plasmapheresis during the study. Patients with a bleeding disorder that was not under adequate control (including a platelet count <50,000 or international normalised ratio [INR] >1.5 for patients who were not on anticoagulant treatment, e.g., warfarin). Patients who were on anticoagulant therapy had to have their anticoagulant status optimised and be on a stable dose for 4 weeks before screening. Patients who were on anticoagulant therapy were not eligible to participate in CSF assessments. Any other medical conditions (e.g., cardiac, respiratory, gastrointestinal, renal disease) which were not stably and adequately controlled, or which in the opinion of the investigator could affect the patient's safety or interfere with the study assessments.

	Participation in a clinical study involving any therapeutic monoclonal antibody, protein derived from a monoclonal antibody, immunoglobulin therapy, or vaccine within six months before screening unless it could be documented that the patient had been randomised to placebo. Participation in a clinical study involving any anti-amyloid therapies (including any monoclonal antibody therapies and any BACE inhibitor therapies) unless it could be documented that the patient only had received placebo. Patients who had any known prior exposure to lecanemab. Patients who had been dosed in a clinical study involving any new chemical entities for AD within six months prior to screening unless it could be documented that the patient had been in a placebo treatment arm. Severe visual or hearing impairment that would have prevented the patient from performing psychometric tests accurately.
Duration of study	Core study: 41 months (27 Mar 2019 to 25 Aug 2022)
Trial drugs	Lecanemab, randomised/completed: 898/729 Placebo, randomised/completed: 897/757

Based on Table 8 of the CS[2]

AChEi = acetylcholinesterase inhibitor; AD = Alzheimer's disease; ADCOMS = Alzheimer's disease composite score; *ApoE4* – apolipoprotein E4; BACE = β-site amyloid precursor protein cleaving enzyme; BMI = body mass index; CDR-SB = Clinical Dementia Rating – Sum of Boxes; CS = company submission; CSF = cerebrospinal fluid; GDS = global deterioration scale; INR = international normalised ratio; MCI = mild cognitive impairment; MMSE = Mini mental state examination; MRI = magnetic resonance imaging NIA-AA = National Institute on Aging and the Alzheimer's Association; OLE = open-label extension; TIA = transient ischaemic attack; UK = United Kingdom; WMS-IV LMII = Wechsler Memory Scale IV Logical Memory (subscale) II

Figure 3.1: Participant flow in Clarity AD



Based on Figure 9 of the CS[2]

AD = Alzheimer's disease; CS = company submission; OLE = open-label extension; PET = positron emission tomography

The decision problem and final NICE scope indicate that lecanemab should be considered as an add-on treatment (in addition to usual care). Table 3.6 provides a summary of the proportions of participants in Clarity AD who were receiving concomitant symptomatic AD treatments; the CS did not provide any details of non-pharmacological interventions received by participants in Clarity AD.[2]

Table 3.6: Concomitant use of symptomatic AD medications in Clarity AD

	Number of patients, n (%)	
	Lecanemab (n=898)	Placebo (n=897)
Patients who took at least one AD medication	[redacted]	[redacted]
Donepezil	[redacted]	[redacted]
Donepezil; memantine	[redacted]	[redacted]
Galantamine	[redacted]	[redacted]
Memantine	[redacted]	[redacted]
Rivastigmine	[redacted]	[redacted]
Based on Table 63, Appendix O of the CS[9] AD = Alzheimer's disease; CS = company submission		

EAG comment: In response to clarification questions,[13] the company provided additional data on the use of symptomatic AD treatments in Clarity AD, separately for the MCI due to AD and mild dementia due to AD populations (Table 3.7), and on non-pharmacological interventions received by participants in Clarity AD (Table 3.8).

Table 3.7: Concomitant use of symptomatic AD medications in Clarity AD by clinical subgroup (MCI and mild AD)

	Number of patients, n (%)			
	Lecanemab (n=898)		Placebo (n=897)	
	MCI (n=[redacted])	Mild AD (n=[redacted])	MCI (n=[redacted])	Mild AD (n=[redacted])
Patients who received an AChEi	[redacted]	[redacted]	[redacted]	[redacted]
Patients who received memantine	[redacted]	[redacted]	[redacted]	[redacted]
Patients who received an AChEi AND memantine	[redacted]	[redacted]	[redacted]	[redacted]
Patients who received a non-pharmacological intervention (e.g., cognitive training, cognitive stimulation, reminiscence therapy)	[redacted]	[redacted]	[redacted]	[redacted]
Patients who received a non-pharmacological intervention AND took an AChEi	N/R	N/R	N/R	N/R
Patients who received a non-pharmacological intervention AND took memantine	N/R	N/R	N/R	N/R
Patients who received a non-pharmacological intervention AND took both an AChEi and memantine	N/R	N/R	N/R	N/R
Based on Table 36, response to clarification[10]				

AChEi = acetylcholinesterase inhibitor; AD = Alzheimer's disease; MCI = mild cognitive impairment; N/R = not recorded

Table 3.8: Concomitant non-pharmacological interventions in Clarity AD by clinical subgroup (MCI and mild AD)

Clinical subgroup	Lecanemab, n	Placebo, n
All patients	[redacted]	[redacted]
MCI due to AD	[redacted]	[redacted]
Mild AD	[redacted]	[redacted]

Based on Table 14, Response to clarification[10]
AD = Alzheimer's disease; MCI = mild cognitive impairment

EAG comment: Based on clinical expert opinion:

- *"I do not know of any reliable current UK data, but my strong impression is that a minority of UK patients with MCI due to AD receive an AChEi and almost none receive memantine",*
- *"I do not know of reliable UK data, but I think most people with mild AD dementia will be offered treatment and about 70% will subsequently take an AChEi and about 5% will take memantine",*

the EAG questions whether the proportions of participants in Clarity AD who were receiving concomitant symptomatic AD medications are likely to be consistent with current UK clinical practice.

[redacted]

Efficacy analyses were performed on the intention-to-treat (ITT) full analysis data set+ (FAS+), and safety analyses on the safety analysis data set (SAS). The ITT FAS+ data set was defined as: *"Randomised patients who received at least one dose of study drug, and who had a baseline assessment and at least one post-dose primary efficacy measurement."*[2] The SAS data set was defined as: *"All allocated patients who received at least one dose of study drug. At least one laboratory, vital sign, or*

ECG measurement obtained subsequent to at least one dose of study drug was required for inclusion in the analysis of each specific parameter. To assess change from baseline, a baseline measurement was also required. This was the analysis population used for all safety analyses which was based on as-treated principle."[2]

The primary objective of Clarity AD was to evaluate the change from baseline in the CDR-SB at 18 months of treatment with lecanemab, compared to placebo, in patients with early AD. Based on Study 201, it was estimated that approximately 1,766 patients would be needed to achieve 90% power to detect the treatment difference between placebo and lecanemab in all patients using a two-sample t-test at a significance level of two-sided alpha = 0.05. The primary analysis was performed using a mixed effects model with repeated measures (MMRM) in the ITT population. The MMRM included treatment group, visit, stratification variables, baseline CDR-SB-by-visit interaction and treatment group-by-visit interaction as fixed effects, and baseline CDR-SB as a covariate. An unstructured covariance matrix was employed to model the covariance of within-patient effect. If the MMRM failed to converge then a covariance structure with fewer parameters was employed. Further details of the analysis methods are provided in the CS (Section B.2.4.2, Table 14).[2]

3.2.2 Management of ARIA

The SmPC for lecanemab (CS, Appendix C)[9] includes the following text [redacted] in relation to amyloid-related imaging abnormalities (ARIA):

"[redacted]"

The CS (Section B.2.3.1.2) provides the following information about the criteria for treatment interruption due to ARIA used in Clarity AD:

"In the Clarity AD core study, any patients who developed a single macrohaemorrhage, multiple (>10) microhaemorrhages cumulatively, symptomatic cerebral microhaemorrhages, or symptomatic superficial siderosis had treatment administration temporarily stopped, and an additional safety visit and MRI at approximately 30 days after radiographic features were first identified. All patients who experienced these events had further safety visits approximately every 30 days until ARIA-H or intracerebral haemorrhage had stabilised radiographically and symptoms (if any) had resolved, then administration of treatment continued. Patients who developed asymptomatic, radiographically mild ARIA-E continued the treatment uninterrupted but had an additional safety visit and MRI at

approximately 30 days, 60 days, and 90 days after the MRI features were first identified. Patients continued with treatment if their ARIA-E did not worsen radiologically and remained asymptomatic. If their ARIA-E developed to a moderate or severe manifestation, or became symptomatic, or patients presented acutely with symptoms or radiographically moderate or severe ARIA-E, patients were temporarily stopped from treatment administration and only resumed treatment if ARIA-E resolved radiographically and symptoms (if any) resolved."[2]

[redacted][9]

3 9 [redacted]

[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

Based on Table 1 of Appendix C of the CS[9]

[redacted]

3 10 [redacted]

[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

Based on Table 2 of Appendix C of the CS[9]

[redacted]

3 11 [redacted]

[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

[redacted]	[redacted]		
	[redacted]	[redacted]	[redacted]
Based on Table 3 of Appendix C of the CS[9] [redacted]			

EAG comment: There appears to be some inconsistency between the reported treatment suspension criteria used in Clarity AD and [redacted][2] [redacted][7] [redacted]

In their clarification response,[10] the company provided the following additional information on treatment suspensions due to ARIA in the Clarity AD study:

"With reference to the recommendations (appendix C.1.4.2 of the CS) [redacted]*, please provide details of:*

a) *The numbers patients, in the Clarity AD study, who met the criteria for dose suspension specified in these recommendations.*

Company response: [redacted] *(*[redacted]*%) patients in the lecanemab arm and* [redacted] *(*[redacted]*%) patients in the placebo arm in Clarity AD met the criteria for dose suspension specified in these recommendations. Details of patients requiring dose suspensions in Clarity AD relating to responses to parts a)-f) of this question are presented in Table 3.12.*

b) *The number patients, in the Clarity AD study, in whom treatment was suspended due to ARIA.*

Company response: *Of those patients,* [redacted] *(*[redacted]*%) patients in the lecanemab arm and* [redacted] *(*[redacted]*%) in the placebo arm had their treatment suspended due to ARIA (Table 3.12).*

c) *The number of patients who experienced more than one suspension of treatment, due to ARIA, during the Clarity AD study.*

Company response: *Of those patients,* [redacted] *(*[redacted]*%) in the lecanemab arm and* [redacted] *(*[redacted]*%) in the placebo arm experienced more than one suspension of treatment due to ARIA (Table 3.12).*

d) *The mean, SD and range of the duration of treatment suspensions due to ARIA experienced by patients in the Clarity AD study.*

Company response: *Mean duration of treatment suspension due to ARIA was* [redacted] *weeks (SD [range]:* [redacted] *[*[redacted]*]) in the lecanemab arm and* [redacted] *weeks (SD [range]:* [redacted] *[*[redacted]*]) in the placebo arm (Table 3.12).*

e) *The numbers of additional MRI scans and clinical assessments undertaken in patients, in the Clarity AD study, in whom treatment had been suspended due to ARIA.*

Company response: *For patients whose treatment was suspended due to ARIA (Table 3.12), the mean number of additional MRI scans required was [redacted] (SD: [redacted]) in the lecanemab arm and [redacted] (SD: [redacted]) in the placebo arm.*

f) The number of patients, in the clarity AD study, in whom dosing was not resumed after suspension and additional monitoring.

Company response: *[redacted] ([redacted]%) and [redacted] ([redacted]%) patients in the lecanemab and placebo arms, respectively, did not resume dosing following suspension and additional monitoring due to ARIA (Table 3.12).*

g) How and to what extent are treatment suspension and additional monitoring are reflected in the economic model?

Company response: *As detailed in the CS, Document B, Section B.3.5.2, mean compliance ([redacted]) for lecanemab was included in the model, informed by Clarity AD. This was defined as (total number of infusions patients actually received) / (total number of infusions the patients could have received), regardless of infusion interruption. As such, treatment suspension due to ARIA would be captured within compliance, and therefore reflected in the treatment acquisition and administration costs in the model.*

Additionally, as detailed in Section B.3.5.5, UK clinical expert opinion was sought to inform management of ARIA events thus informing AE management costs in the model. Based on the clinicians' feedback, management of ARIA was not expected to differ between ARIA-E and ARIA-H. For mild-moderate ARIA events, clinical assessment and two additional MRI scans would be required. For severe-serious ARIA events, management included four additional MRI scans alongside clinical assessment and hospitalisation. The cost of this additional monitoring and the duration, where relevant, is reflected in AE management costs in the model."

Table 3.12: Dose suspension due to ARIA events in Clarity AD core study, SAS

	Placebo (n=897) n (%)	**Lecanemab (n=898) n (%)**	**Total (n=1795) n (%)**
Subjects who met the criteria for dose suspension specified in the draft SmPC[a]	[redacted]	[redacted]	[redacted]
Subjects in whom treatment was suspended due to ARIA[b,c]	[redacted]	[redacted]	[redacted]
Subjects who experienced more than one suspension of treatment due to ARIA[d,e]	[redacted]	[redacted]	[redacted]
Duration of treatment suspensions due to ARIA[f] (weeks)			
Mean (SD)	[redacted]	[redacted]	[redacted]
Range[g]	[redacted]	[redacted]	[redacted]
Number of additional MRI scans in whom treatment had been suspended due to ARIA			
Mean (SD)	[redacted]	[redacted]	[redacted]
Range[h]	[redacted]	[redacted]	[redacted]
Subjects in whom dosing was not resumed after suspension and additional monitoring[e]	[redacted]	[redacted]	[redacted]

Based on Table 46, Response to clarification[10]
a) TE symptomatic ARIA-E with moderate or severe in clinical severity or in radiographic severity, TE asymptomatic ARIA-E with moderate or severe in radiographic severity, TE symptomatic ARIA-H (MH, SS), or TE asymptomatic ARIA-H (MH, SS) with moderate or severe in radiographic severity.
b) Included both study treatment interruption and study treatment discontinuation. Any missed doses after ARIA led to study treatment interruption and study treatment discontinuation and until resumption of treatment are considered as suspension of treatment due to ARIA.
c) Percentage is based on # of subjects who met the criteria for dose suspension specified in the draft SmPC.
d) Counted if subject had second or more suspension of treatment after resumption of treatment.
e) Percentage is based on # of subjects in whom treatment was suspended due to ARIA
f) Missed doses are counted by last scheduled visit. Duration is calculated using the number of missed doses x 2 weeks. Total duration is used if subjects had more than one suspension of treatment due to ARIA.
g) [redacted] subjects ([redacted]) had no scheduled visit where subject could have treatment after ARIA, which shows 0 in duration of treatment suspension.
h) [redacted] subjects ([redacted]) had no additional MRI scans because ARIA-E resolved one month after onset and scheduled visit MRI could cover follow-up MRI, which shows 0 in number of additional MRI scans.
AD = Alzheimer's disease; ARIA = amyloid-related imaging abnormality; ARIA-E = amyloid-related imaging abnormality-oedema/effusion; ARIA-H = amyloid-related imaging abnormality-haemorrhage; LEC10-BW = lecanemab 10 g/kg biweekly; MH = microhaemorrhage, MRI = magnetic resonance imaging; PBO = placebo; SAS = safety analysis set; SD = standard deviation; SmPC = summary of product characteristics; SS = superficial siderosis; TE = treatment-emergent

3.2.3 Baseline characteristics of participants in Clarity AD

The baseline characteristics of participants in Clarity AD are presented in Table 3.13; these data appear to be for the SAS population.

Of the 1,795 patients in the SAS, patients were predominantly white ([redacted]%) with a mean age of [redacted] years. The proportion of patients with MCI and mild AD was similar between the lecanemab and placebo arms. Gender, categorical *ApoE4* genotype, and duration of disease/symptoms were also well balanced between the two groups.

Table 3.13: Clarity AD patient demographics and baseline characteristics

	Lecanemab (n=898)	Placebo (n=897)	Total patients (1,795)
Mean age, years (SD) [a]	[redacted]	[redacted]	[redacted]
Female, n (%)	[redacted]	[redacted]	[redacted]
Race, n (%)			
White	[redacted]	[redacted]	[redacted]
Black or African American	[redacted]	[redacted]	[redacted]
Asian	[redacted]	[redacted]	[redacted]
American Indian or Alaska native	[redacted]	[redacted]	[redacted]
Native Hawaiian or other Pacific Islander	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]
Not reported	[redacted]	[redacted]	[redacted]
***ApoE4* carrier status (Laboratory), n (%)**			
Carriers	[redacted]	[redacted]	[redacted]
Heterozygous	[redacted]	[redacted]	[redacted]
Homozygous	[redacted]	[redacted]	[redacted]

	Lecanemab (n=898)	Placebo (n=897)	Total patients (1,795)
Use of AD symptomatic medication at baseline (CRF), n (%)			
Yes	[redacted]	[redacted]	[redacted]
Clinical subgroup (CRF), n (%)			
MCI due to AD	[redacted]	[redacted]	[redacted]
Mild AD dementia	[redacted]	[redacted]	[redacted]
Number of years of disease since diagnosis			
n	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]
Median (range)	[redacted]	[redacted]	[redacted]
Number of years since onset of symptoms			
n	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]
Median (range)	[redacted]	[redacted]	[redacted]
Age at onset of symptoms (years)			
n	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]
Median (range)	[redacted]	[redacted]	[redacted]

Based on Table 10 of the CS[2]
Percentages are based on the total number of patients in relevant treatment group.
[a]Age was calculated at date of informed consent.
AD = Alzheimer's disease; *ApoE4* = apolipoprotein E4; CRF = case report form; CS = company submission; MCI = mild cognitive impairment; SD = standard deviation

The CS (Section B.2.3.3) states that: *"Baseline characteristics from the primary trial publication[25] (as listed in Appendix N) were presented to UK clinical experts in an advisory board held in May 2023 and the Clarity AD population was deemed generalisable to UK clinical practice."*

EAG comment: The EAG notes that the data provided in Appendix N of the CS[9] reports use of symptomatic AD medication only in aggregate (across the combined MCI due to AD and mild dementia due to AD populations). Since UK recommendations and practice differ between these two groups, the EAG questions whether the UK clinical experts participating in the advisory board were provided with sufficient information to assess the generalisability of Clarity AD to UK practice.

3.2.4 Quality of the Clarity AD study

The CS (Section B.2.5) provided an assessment of the methodological quality of the Clarity AD study (Table 3.14).

Table 3.14: Clarity AD quality assessment results

Questions	Clarity AD
Was randomisation carried out appropriately?	**Yes:** Patients were assigned to treatments, (allocated 1:1; lecanemab:placebo), based on a computer-generated randomisation scheme that was reviewed and approved by an independent statistician. Patients were stratified according to clinical subgroup; presence or absence of ongoing approved AD treatment (e.g., AChEis, memantine, or both); *APoE4* status (i.e., *APoE4* carrier or noncarrier); and geographical region.
Was the concealment of treatment allocation adequate?	**Yes.** Randomisation data was kept strictly confidential, filed securely by an appropriate group with the sponsor or CRO and accessible only to authorised persons (e.g., Eisai Global Safety) until the time of unblinding, per SOP.
Were the groups similar at the outset of the study in terms of prognostic factors?	**Yes:** There was no significant difference in the baseline characteristics reported between the treatment arms.
Were the care providers, participants, and outcome assessors blind to treatment allocation?	**Yes:** During the core study phase, patients and all personnel involved with the conduct and interpretation of the study, including investigators, site personnel, and sponsor staff were blinded to the treatment codes.
Were there any unexpected imbalances in dropouts between groups?	**No:** There were no unexpected imbalances in dropouts between groups. Withdrawals by patient were similar in both arms (lecanemab 169/898 [18.8%]; placebo 140/897 [15.6%]).
Is there any evidence to suggest that the authors measured more outcomes than they reported?	**No:** No evidence to suggest that the authors measured more outcomes than they reported.
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	**Yes:** Efficacy analysis was performed using the FAS population. Following the intention-to-treat principle, patients were analysed according to the treatments and strata to which they were assigned at randomisation. For missing data: Missing values in all endpoint data were handled by the MMRM. Other statistical methods for missing data were also performed as sensitivity analyses

Source: Table 15, CS[2]
AChEi = acetylcholinesterase inhibitor; AD = Alzheimer's disease; *APoE4* = apolipoprotein E4; CRO = contract research organisation; CS = company submission; FAS = full analysis set; MMRM = mixed effects model with repeated measures; SOP = standard operating procedure

EAG comment: The EAG agrees with the company's assessment of the methodological quality of the Clarity AD study.

3.2.5 Effectiveness results of Clarity AD

The CS included results, from Clarity AD, for the primary outcome measure CDR-SB, for additional secondary outcome measures of cognition and function (ADAS-Cog 14, ADCOMS and ADCS MCI-ADL), and for exploratory HRQoL and disease progression outcomes.[2] The CS also included efficacy data on amyloid levels,[2] which have not been included in this report because amyloid levels were not an outcome measure specified in the final NICE scope.[3]

3.2.5.1 Primary efficacy outcome CDR-SB

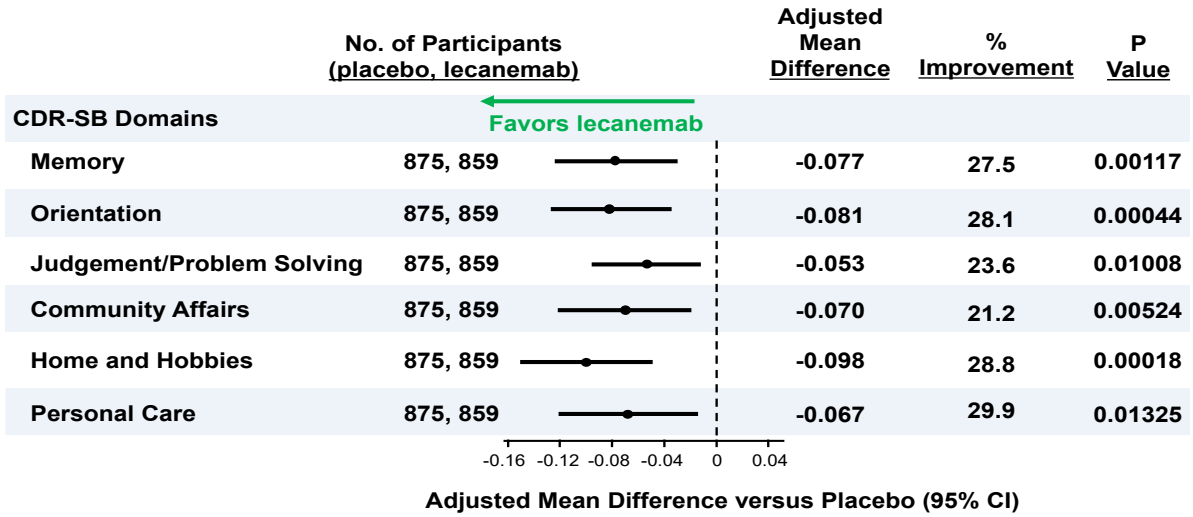
The primary endpoint was the adjusted mean difference of the change from baseline in CDR-SB at 18 months between lecanemab and placebo in the ITT FAS+. Lecanemab treatment was associated with numerically small, but statistically significant benefits across all six domains of CDR-SB (memory, orientation, judgement/problem solving, community affairs, home and hobbies, and personal care).[2] The adjusted mean difference in change from baseline, for lecanemab versus placebo, at 18 months, for overall CDR-SB, was -0.451 (95% confidence interval [CI]: -0.669 to -0.233), which the CS noted reflected a 27.1% reduction in decline.[2]

Table 3.15: Change from baseline in CDR-SB Score at 18 Months – MMRM – ITT FAS+

CDR-SB	Lecanemab (n=859)	Placebo (n=875)
Number of patients included in the MMRM	859	875
N (week 79)	714	757
Baseline mean (SD)	[redacted]	[redacted]
18-month mean (SD)	[redacted]	[redacted]
Adjusted mean change from baseline in MMRM (SE)	1.213 (0.082)	1.663 (0.080)
Adjusted mean difference in change from baseline (lecanemab – placebo)	-0.451	
95% CI for differences	-0.669, -0.233	
p-value	0.00005	
% Difference vs. placebo	-27.1%	

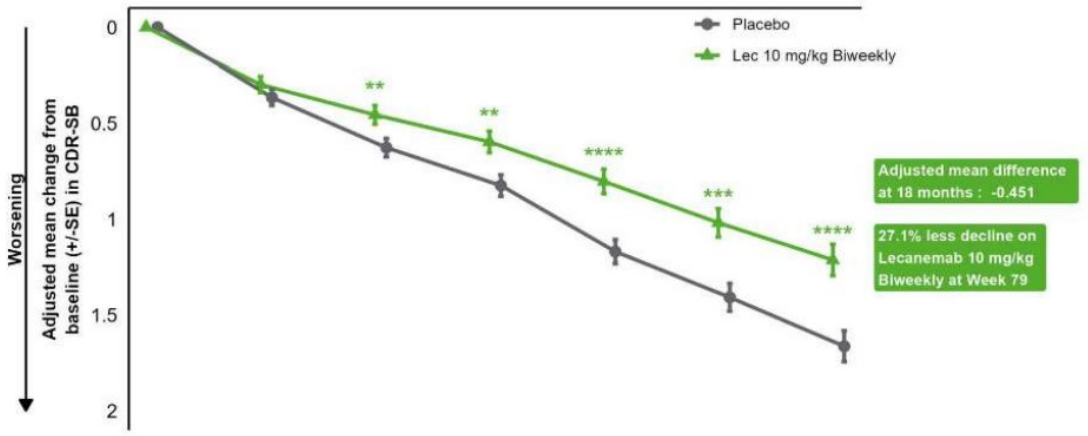
Based on Table 26, Response to clarification[10]
CDR-SB = Clinical Dementia Rating - Sum of Boxes; CI = confidence interval; FAS = full analysis set; MMRM = mixed model for repeated measures; SD = standard deviation; SE = standard error; ITT = intention-to-treat

Figure 3.2: Adjusted mean difference versus placebo in CDR-SB by domain – ITT FAS+



Based on Figure 11, CS[2]
CDR-SB = Clinical Dementia Rating – Sum of Boxes; CI = confidence interval; CS = company submission; FAS = full analysis set; ITT = intention-to-treat

Figure 3.3: Adjusted mean change (±SE) from baseline in CDR-SB – ITT FAS+



	Baseline	Week 13	Week 27	Week 39	Week 53	Week 65	Week 79
Placebo	875	849	828	813	779	767	757
Lec 10 mg/kg Biweekly	859	824	798	779	765	738	714

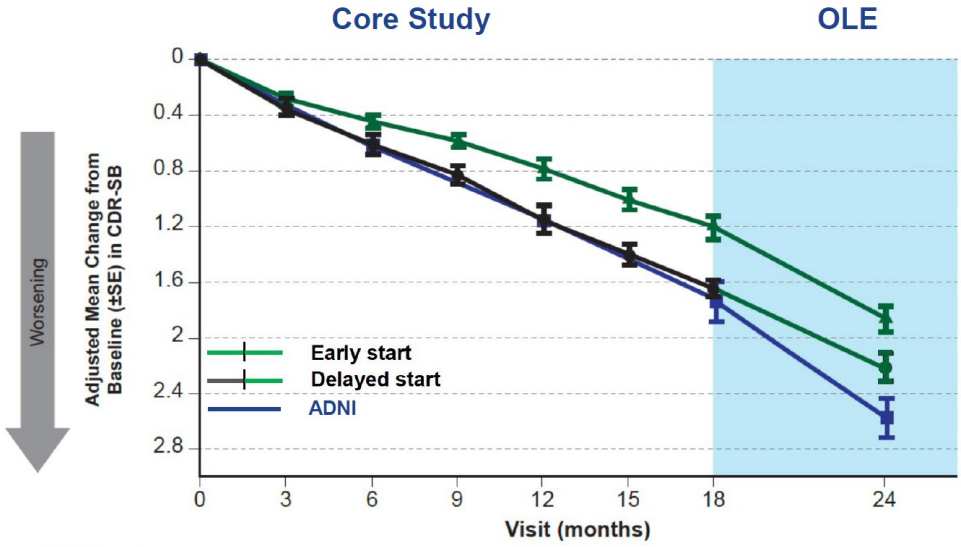
Based on Figure 12, CS[2]
** $p<0.01$, *** $p<0.001$, **** $p<0.0001$
CDR-SB = Clinical Dementia Rating – Sum of Boxes; CS = company submission; FAS = full analysis set; ITT = intention-to-treat; kg = kilogram; Lec = lecanemab; mg = milligram; SE = standard error

EAG comment: The EAG notes that the results of the Clarity AD trial indicated that patients treated with lecanemab experienced smaller changes from baseline (slower decline) than those in the placebo group, for all six cognition and function domains of the CDR-SB, however, the absolute difference in change between the treatment and placebo groups was small. Studies cited in the CS[26, 27] in support of the clinical significance of the treatment effect indicate that an increase of between 1 and 2 points on CDR-SB would be considered a clinically significant decline; the reported adjusted mean between group difference in change from baseline was -0.451 over 18 months. The EAG also notes the European Medicines Agency (EMA) comment, quoted in a 'data on file' reference:[28] "[redacted]" The EAG therefore considers the clinical significance of the observed treatment effects of lecanemab to be uncertain. The EAG sought clinical expert opinion regarding what % reduction in decline, compared to placebo, would be considered clinically meaningful and received the following response: *"This is problematic and likely to be different at different disease stages. Importantly, Individual patients/families will have very different views on what is meaningful for them, depending on their differing values and expectations. When deciding whether to prescribe lecanemab, I would be strongly influenced by their views in each individual case. I think somewhere between 20 and 40% would apply for most people and so sounds about right to me, but this benefit would have to outweigh treatment burden and risks. In oncology, a 20-30% benefit in the right direction seems to be considered clinically meaningful without any question. The absolute difference of 0.45 on CDR-SB is about the same as achieved by existing anticholinesterase drugs for AD (that are symptomatic rather than influencing rate of decline) and most people now believe their benefit is clinically meaningful. This is despite the size of effect being less than the cited minimum clinically important difference of >1"*[12]

In its clarification response, the company provided initial results from the OLE for a non-inferiority test between early start lecanemab and delayed start lecanemab, indicating that at 24-months, there was

[redacted]% less decline on adjusted mean change from baseline in CDR-SB for the early start lecanemab group compared with the delayed start lecanemab group.[10] Non-inferiority criteria were met at 24 months for these groups, with the lower bound of 1-sided 90% CI being greater than 0 (90% CI: [redacted]).[10] The interim efficacy results for CDR-SB were also compared with an observational cohort from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database. In this analysis, participants from ADNI were matched with the Clarity AD population based on baseline demographics and clinical characteristics, including randomisation strata. During the core study period, the adjusted mean change from baseline in CDR-SB in the ADNI cohort was similar to the placebo arm. Beyond 18 months, the rate of decline in the ADNI cohort was greater than the delayed start group, consistent with the latter receiving lecanemab from this time point.[10]

Figure 3.4: Change in CDR-SB Score through 24 months in Clarity AD OLE study



Based on Figure 1, response to clarification[10]
AD = Alzheimer's disease; ADNI = Alzheimer's Disease Neuroimaging Initiative; CDR-SB = Clinical Dementia Rating - Sum of Boxes; OLE = open-label extension; SE = standard error

EAG comment: The EAG notes that, from visual examination of Figure 3.4, there appears to be an acceleration of decline after the 18-month time point (OLE), but that this acceleration appears to be common to both lecanemab-treated and untreated (ADNI) patients, such that the treatment effect of lecanemab appears to be maintained. However, the EAG considers that currently available data are insufficient to adequately demonstrate the long-term efficacy of lecanemab.

3.2.5.2 Secondary efficacy outcome ADAS-Cog 14

The ADAS-Cog14 is a scale that directly measures how a patient thinks and feels and consists of 14 tasks that include both patient-completed tests and observer-based assessments that assess memory, language, and praxis. Lecanemab treatment was associated with a numerically small, but statistically significant benefit with respect to overall ADAS-Cog 14 score.[2] The adjusted mean difference in change from baseline, for lecanemab versus placebo, at 18 months, for overall ADAS-Cog 14, was -1.442 (95% CI: -2.270 to -0.613), which the CS noted reflected a 25.8% reduction in decline.[2]

Table 3.16: Change from baseline in ADAS-Cog14 at 18 months – MMRM, core study, ITT FAS+

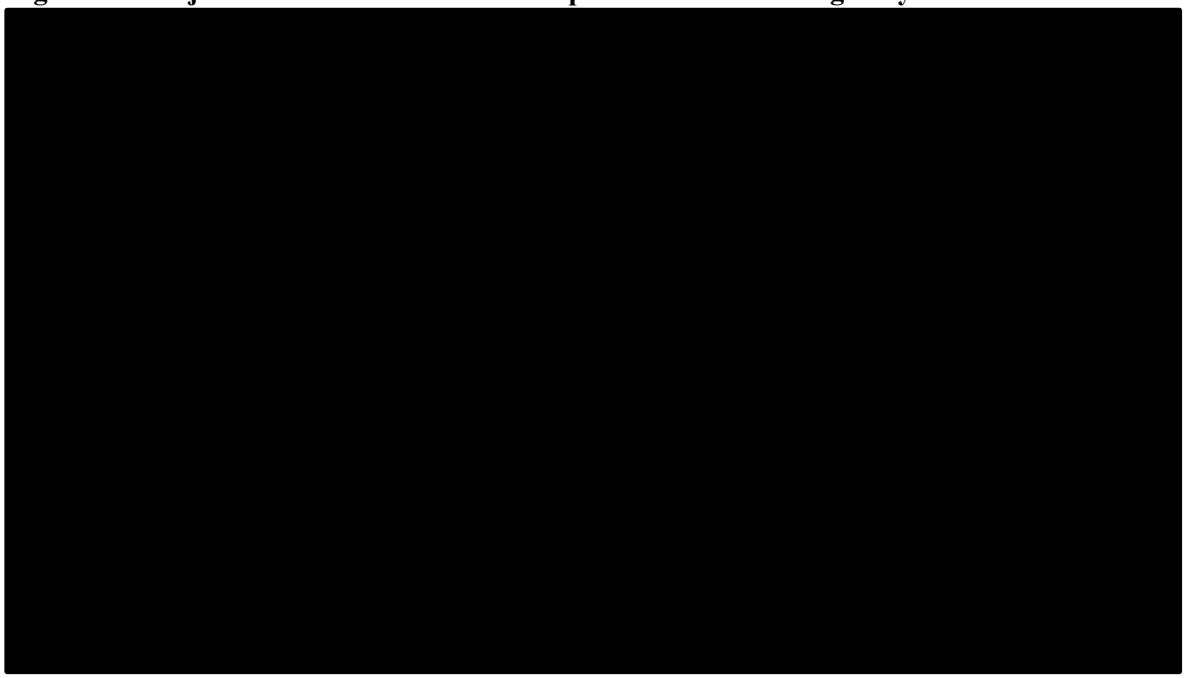
ADAS-Cog14	Lecanemab (n=859)	Placebo (n=875)

Number of patients included in the MMRM	856	873
N (week 79)	705	740
Baseline mean (SD)	[redacted]	[redacted]
18-month mean (SD)	[redacted]	[redacted]
Adjusted mean change from baseline in MMRM (SE)	4.140 (0.314)	5.581 (0.309)
Adjusted mean difference in change from baseline (lecanemab – placebo)	-1.442	
95% CI for differences	-2.270, -0.613	
p-value	0.00065	
% Difference vs. placebo	-25.8%	

Based on Table 27, Response to clarification[10]
ADAS-Cog14 = Alzheimer's Disease Assessment Scale - Cognitive Subscale 14-item version; CI = confidence interval; FAS = full analysis set; ITT = intention-to-treat; MMRM = mixed model for repeated measures; SD = standard deviation; SE = standard error;

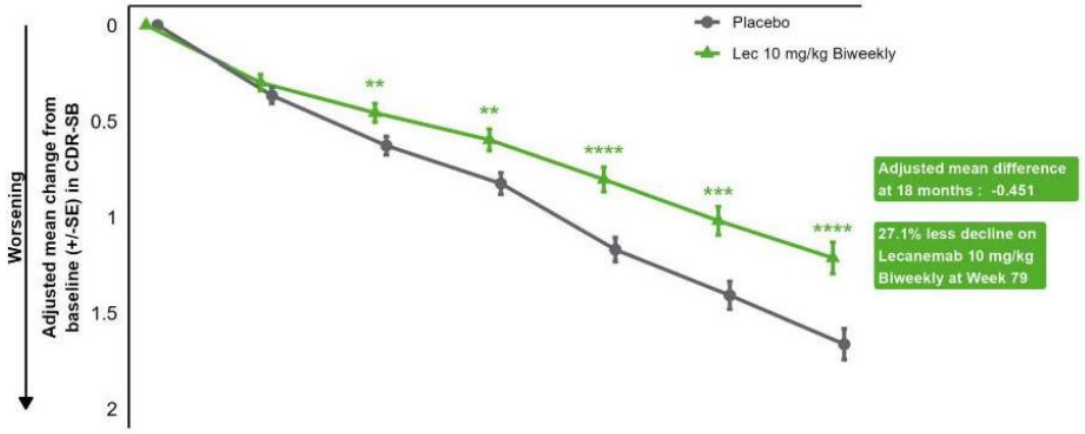
The apparent beneficial effects of lecanemab were not consistent across all components of ADAS-Cog 14, however, the direction of effect was generally in favour of lecanemab (Figure 3.5).

Figure 3.5: Adjusted mean difference versus placebo in ADAS-Cog14 by item – ITT FAS+



Based on Figure 17, CS[2]
ADAS-Cog14 = Alzheimer's Disease Assessment Scale – Cognitive Subscale 14-item version; CI = confidence interval; CS = company submission; FAS+ = full analysis set; ITT = intention-to-treat

Figure 3.6: Change from baseline in ADAS-Cog14 at interim timepoints ITT FAS+

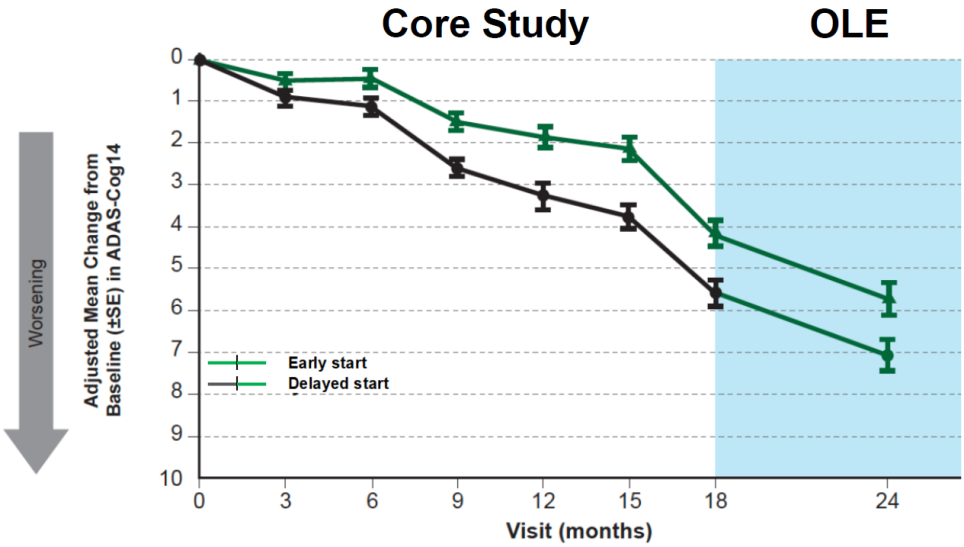


	Baseline	Week 13	Week 27	Week 39	Week 53	Week 65	Week 79
Placebo	875	849	828	813	779	767	757
Lec 10 mg/kg Biweekly	859	824	798	779	765	738	714

Based on Figure 16, CS[2]
* $p<0.05$, ** $p<0.01$, *** $p<0.001$, **** $p<0.0001$, ***** $p<0.00001$
ADAS-Cog14 = Alzheimer's Disease Assessment Scale = Cognitive Subscale 14-item version; CS = company submission; FAS = full analysis set; ITT = intention-to-treat; kg = kilogram; Lec = lecanemab; mg = milligram; SE = standard error

In response to clarification questions,[10] the company provided initial results (24 months) from the OLE for a non-inferiority test between early start lecanemab and delayed start lecanemab.

Figure 3.7: Change in ADAS-Cog14 score through 24 months in Clarity AD OLE study



(N) Placebo:	872	844	823	807	770	762	738	633
(N) Lecanemab:	854	819	793	771	753	730	703	630
(N) Early Start:	854	819	793	771	753	730	703	630

Based on Figure 2, Response to clarification[10]
AD = Alzheimer's Disease; ADAS-Cog14 = Alzheimer's Disease Assessment Scale – Cognitive Subscale 14; OLE = open-label extension; SE = standard error

3.2.5.3 Secondary efficacy outcome ADCOMS

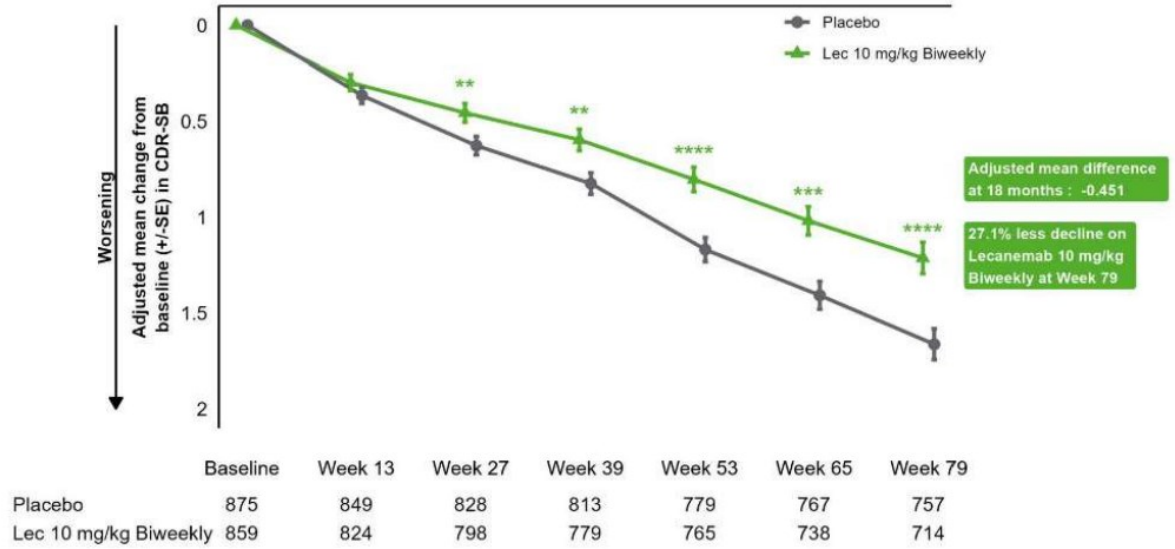
Alzheimer's Disease Composite Score is a composite clinical outcome consisting of four ADAS-Cog subscale items, two MMSE items, and six CDR-SB items. Lecanemab treatment was associated with a numerically small, but statistically significant benefit with respect to overall ADCOMS score.[2] The adjusted mean difference in change from baseline, for lecanemab versus placebo, at 18 months, for overall ADCOMS 14, was -0.05 (95% CI: -0.074 to -0.027), which the CS noted reflected a 23.5% reduction in decline.[2]

Table 3.17: Change from baseline in ADCOMS at 18 months – MMRM, Clarity AD core study, ITT FAS+

ADCOMS	Lecanemab (n=859)	Placebo (n=875)
Number of patients included in the MMRM	859	875
N (week 79)	705	749
Baseline mean (SD)	[redacted]	[redacted]
18-month mean (SD)	[redacted]	[redacted]
Adjusted mean change from baseline in MMRM (SE)	0.164 (0.009)	0.214 (0.009)
Adjusted mean difference in change from baseline (lecanemab – placebo)	-0.050	
95% CI for differences	-0.074, -0.027	
p-value	0.00002	
% Difference vs. placebo	-23.5%	

Based on Table 28, Response to clarification[10]
AD = Alzheimer's disease; ADCOMS = Alzheimer's Disease Composite Score; CI = confidence interval; FAS = full analysis set; ITT = intention-to-treat; MMRM = mixed model for repeated measures; SD = standard deviation; SE = standard error

Figure 3.8: Change from baseline in ADCOMS – ITT FAS+



Based on Figure18, CS[2]
ADCOMS = Alzheimer's Disease Composite Score; CS = company submission; FAS = full analysis set; ITT = intention-to-treat; kg = kilogram; Lec = lecanemab; mg = milligram; SE = standard error

The CS[2] and response to clarification[10] did not include any question-level efficacy results of any results from the OLE, for ADCOMS.

3.2.5.4 Secondary efficacy outcome ADCS-ADL-MCI

The ADCS-ADL-MCI is an 18-item scale that directly measures how a patient functions with respect to activities of daily living. Lecanemab treatment was associated with a numerically small, but statistically significant benefit with respect to overall ADCS MCI-ADL score.[2] The adjusted mean difference in change from baseline, for lecanemab versus placebo, at 18 months, for overall ADCS-ADL-MCI, was 2.016 (95% CI: 1.208 to 2.823), which the CS noted reflected a 36.6% reduction in decline.[2]

Table 3.18: Change from baseline in ADCS-ADL-MCI at 18 months – MMRM, Clarity AD core study, ITT FAS+

ADCS-ADL-MCI	Lecanemab (n=859)	Placebo (n=875)
Number of patients included in the MMRM	808	822
N (week 79)	715	754
Baseline mean (SD)	[redacted]	[redacted]
18-month mean (SD)	[redacted]	[redacted]
Adjusted mean change from baseline in MMRM (SE)	-3.484 (0.313)	-5.500 (0.308)
Adjusted mean difference in change from baseline (lecanemab – placebo)	2.016	
95% CI for differences	1.208, 2.823	
p-value	<.00001	
% Difference vs. placebo	-36.6%	

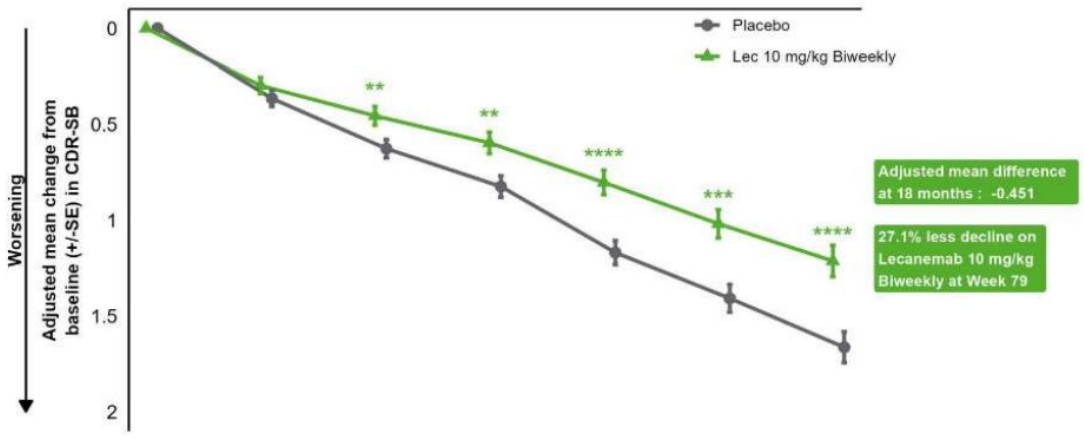
Based on Table 29, Response to clarification[10]
ADAS-Cog14 = Alzheimer's Disease Assessment Scale = Cognitive Subscale 14-item version; ADCS-ADL-MCI = Alzheimer's Disease Cooperative Study-Activities of Daily Living Scale for Mild Cognitive Impairment; CI = confidence interval; FAS = full analysis set; ITT = intention-to-treat; MMRM = mixed model for repeated measures; SD = standard deviation; SE = standard error

The apparent beneficial effects of lecanemab were not consistent across all components of ADCS-ADL-MCI- 14, however, the direction of effect was generally in favour of lecanemab (Figure 3.9).

Figure 3.9: Adjusted mean difference versus placebo in ADCS-ADL-MCI by item – ITT FAS+

Based on Figure 20, CS[2]
ADCS MCI-ADL = Alzheimer's Disease Cooperative Study-Activities of Daily Living Scale for Mild Cognitive Impairment; CI = confidence interval; CS = company submission; FAS = full analysis set; ITT = intention-to-treat; MMRM = mixed model for repeated measures

Figure 3.10: Change from baseline in ADCS-ADL-MCI at interim timepoints – ITT FAS+

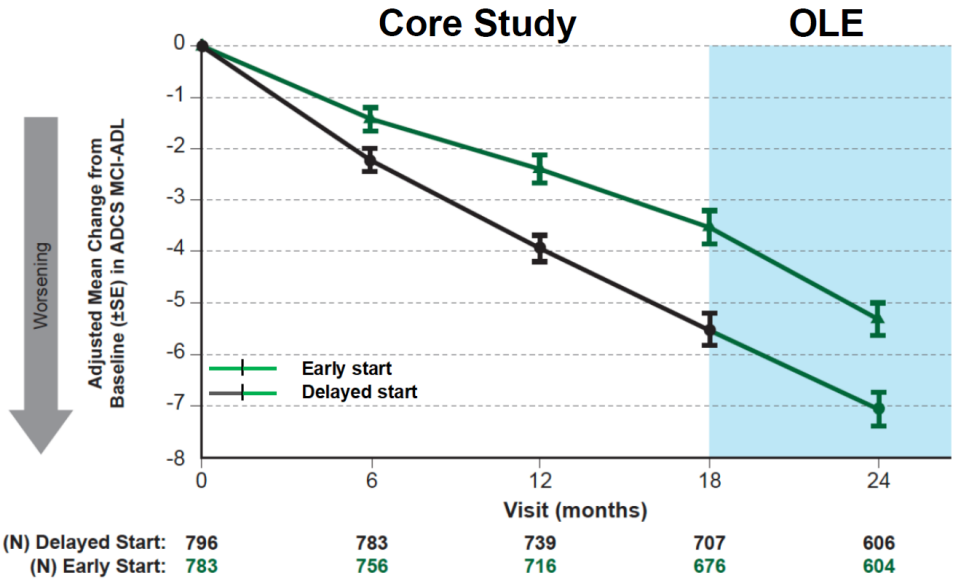


	Baseline	Week 13	Week 27	Week 39	Week 53	Week 65	Week 79
Placebo	875	849	828	813	779	767	757
Lec 10 mg/kg Biweekly	859	824	798	779	765	738	714

Based on Figure 19, CS[2]
** $p<0.01$, ***** $p<0.00001$
ADCS-ADL-MCI = Alzheimer's Disease Cooperative Study-Activities of Daily Living Scale for Mild Cognitive Impairment; FAS = full analysis set; ITT = intention-to-treat; kg = kilogram; Lec = lecanemab; mg = milligram; SE = standard error

In response to clarification questions,[10] the company provided initial results (24 months) from the OLE for a non-inferiority test between early start lecanemab and delayed start lecanemab.

Figure 3.11: Change in ADCS-ADL-MCI score through 24 months in Clarity AD OLE study



Based on Figure 3, Response to clarification[10]
AD = Alzheimer's Disease; ADCS-ADL-MCI = Alzheimer's Disease Cooperative Study-Activities of Daily Living Inventory Mild Cognitive Impairment Version; OLE = open-label extension; SE = standard error

3.2.5.5 Exploratory Outcome, time to progression based on global CDR score

Time to worsening of global CDR score was defined as time from randomisation to worsening of the global CDR score (i.e., the first increase from baseline by at least 0.5 points on the global CDR score in two consecutive visits). In the lecanemab group, [redacted]% of patients had experienced a worsening of global CDR at three months, increasing to only [redacted]% at 18 months. In comparison, [redacted]% of patients in the placebo group had experienced a worsening of global CDR at three months, increasing to [redacted]% at 18 months.[2] At 18 months, lecanemab showed a statistically significant reduction in the risk of progression to the next stage of AD on the global CDR score by 31%, hazard ratio (HR) 0.69 (95% CI: 0.57 to 0.83).[2]

Additional information on rates of progression between disease stages (MCI due to AD to mild, moderate and severe dementia due to AD, and mild dementia due to AD to moderate and severe dementia due to AD), over the course of the core Clarity AD study, was provided in response to clarification questions (Table 3.19).[10]

Table 3.19: Progression from MCI due to AD and mild AD health states within Clarity AD as defined by global CDR by visit, core study, ITT FAS+

Visit	Baseline state	Proportion, n		Health state at corresponding visit	Proportion, n (%)	
		Placebo	Lecanemab		Placebo	Lecanemab
Week 13	MCI due to AD	[redacted]	[redacted]	Mild AD	[redacted]	[redacted]
				Moderate AD	[redacted]	[redacted]
				Severe AD	[redacted]	[redacted]
	Mild AD	[redacted]	[redacted]	Moderate AD	[redacted]	[redacted]

Visit	Baseline state	Proportion, n		Health state at corresponding visit	Proportion, n (%)	
		Placebo	Lecanemab		Placebo	Lecanemab
				Severe AD	[redacted]	[redacted]
Week 27	MCI due to AD	[redacted]	[redacted]	Mild AD	[redacted]	[redacted]
				Moderate AD	[redacted]	[redacted]
				Severe AD	[redacted]	[redacted]
	Mild AD	[redacted]	[redacted]	Moderate AD	[redacted]	[redacted]
				Severe AD	[redacted]	[redacted]
Week 39	MCI due to AD	[redacted]	[redacted]	Mild AD	[redacted]	[redacted]
				Moderate AD	[redacted]	[redacted]
				Severe AD	[redacted]	[redacted]
	Mild AD	[redacted]	[redacted]	Moderate AD	[redacted]	[redacted]
				Severe AD	[redacted]	[redacted]
Week 53	MCI due to AD	[redacted]	[redacted]	Mild AD	[redacted]	[redacted]
				Moderate AD	[redacted]	[redacted]
				Severe AD	[redacted]	[redacted]
	Mild AD	[redacted]	[redacted]	Moderate AD	[redacted]	[redacted]
				Severe AD	[redacted]	[redacted]
Week 65	MCI due to AD	[redacted]	[redacted]	Mild AD	[redacted]	[redacted]
				Moderate AD	[redacted]	[redacted]
				Severe AD	[redacted]	[redacted]
	Mild AD	[redacted]	[redacted]	Moderate AD	[redacted]	[redacted]
				Severe AD	[redacted]	[redacted]
Week 79	MCI due to AD	[redacted]	[redacted]	Mild AD	[redacted]	[redacted]
				Moderate AD	[redacted]	[redacted]
				Severe AD	[redacted]	[redacted]
	Mild AD	[redacted]	[redacted]	Moderate AD	[redacted]	[redacted]
				Severe AD	[redacted]	[redacted]
Week 81	MCI due to AD	[redacted]	[redacted]	Mild AD	[redacted]	[redacted]
				Moderate AD	[redacted]	[redacted]
				Severe AD	[redacted]	[redacted]
	Mild AD	[redacted]	[redacted]	Moderate AD	[redacted]	[redacted]
				Severe AD	[redacted]	[redacted]

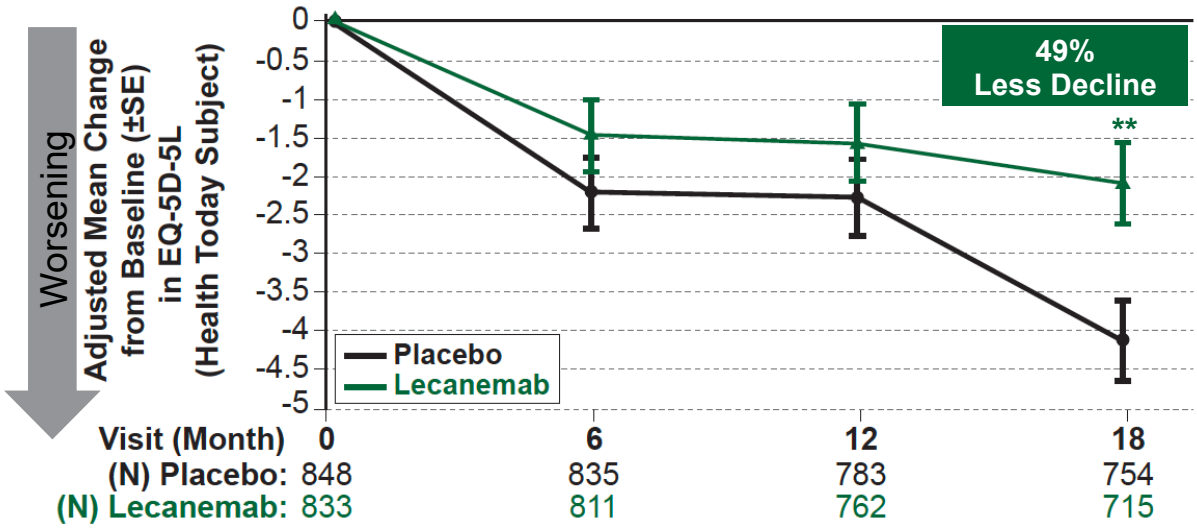
Based on Based on Table 35, Response to clarification[10]
AD = Alzheimer's disease; CDR = Clinical Dementia Rating; FAS = full analysis set; ITT = intention-to-treat; MCI = mild cognitive impairment

EAG comment: The EAG notes that, by week 81, the rates of progression (between all stages) were lower for lecanemab-treated patients than for those in the placebo group.

3.2.5.6 Exploratory HRQoL outcomes

Clarity AD included assessments of the effect of lecanemab treatment of EQ-5D-5L and QOL-AD, both directly (patient-reported) and using partner as a proxy. The adjusted mean difference for lecanemab compared to placebo in the Patient's Survey at 18 months (2.017) was highly statistically significant, representing 49.1% less decline (p=0.00383), (Figure 3.12).[2]

Figure 3.12: Adjusted mean change from baseline in EQ-5D-5L, Health today (VAS subtotal), patient-reported



Based on Figure 23, CS[2]

** p<0.01

EQ-5D-5L = European Quality of Life-5 Dimensions; SE = standard error; VAS = visual analogue scale

However, results from the Partner as a Proxy survey indicated [redacted] between lecanemab-treated patients and those in the placebo group, at 18 months; adjusted mean difference [redacted].[2]

For QOL-AD, there was greater consistency between the results of the Patient's Survey and those from the Partner as a Proxy survey, although the Partner as a Proxy derived estimate still indicated a smaller treatment benefit. The adjusted mean difference for lecanemab compared to placebo in the Patient's Survey at 18 months (0.657) was highly statistically significant, equating to 55.6% less decline (p=0.00231). The adjusted mean difference between lecanemab and placebo in the Partner as a Proxy survey at 18 months (0.535) was statistically significant, equating to 22.9% less decline, p=0.02558.[2]

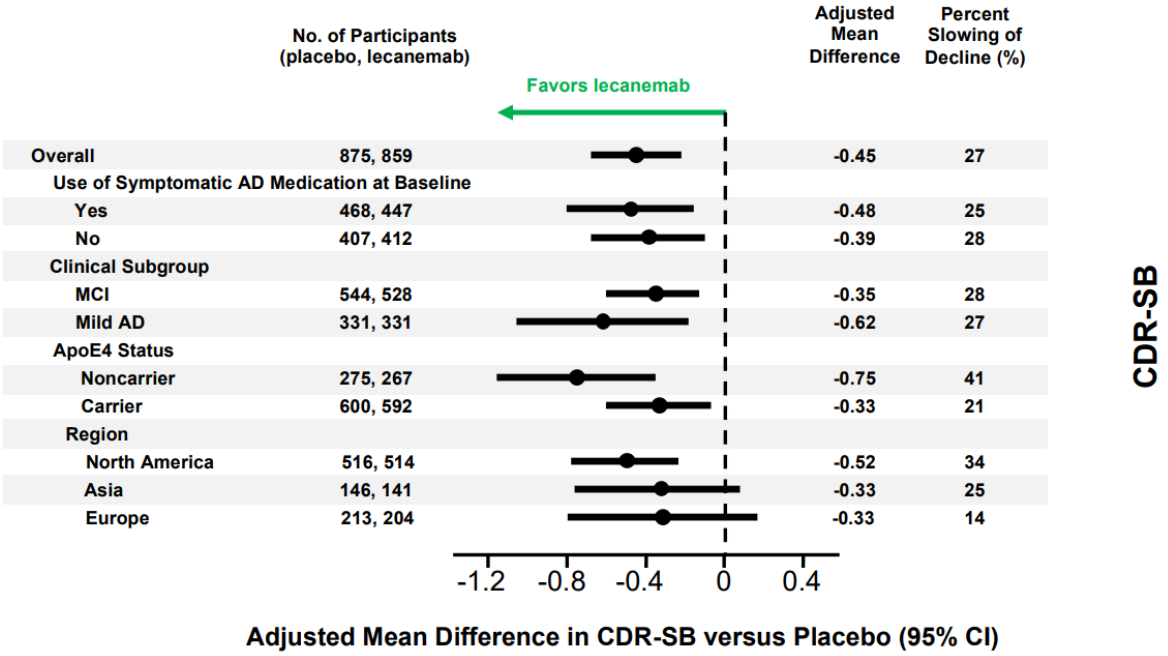
Clarity AD also assessed the effect of lecanemab treatment on caregiver burden (Zarit's Burden Interview). The adjusted mean difference between lecanemab compared to placebo at 18 months (-2.211) was highly statistically significant, equating to 38.4% less decline, p=0.00002, with the direction of effect favouring lecanemab across all 22 domains.[2]

3.2.6 Subgroup analyses of Clarity AD results

3.2.6.1 Baseline disease stage (MCI due to AD and mild dementia due to AD)

The results of subgroup analyses (Appendix E of the CS) indicated that the effects of lecanemab on the primary outcome (CDR-SB), at 18 months, were similar across the two baseline disease stage subgroups.[9]

Figure 3.13: Subgroup analysis for adjusted mean difference in CDR-SB – ITT FAS+, randomisation strata



Based on Figure 8, Appendix E of the CS[9]
Note: Subgroups with <10 subjects in any treatment group are not displayed.
AD = Alzheimer's Disease; CDR-SB = Clinical Dementia Rating - Sum of Boxes; CI = confidence interval; CS = company submission; FAS = full analysis set; ITT = intention-to-treat; MCI = mild cognitive impairment

Similar results were reported for the secondary cognitive and functional outcomes (ADAS-Cog 14, ADCOMS, and ADCS-ADL-MCI).[9]

In response to clarification questions, the company provided further subgroup analyses for those study participants where the standard of care (SoC) comparator matched that specified in the NICE final scope (i.e., participants with MCI due to AD who were without symptomatic AD medication at baseline and participants with mild dementia due to AD who were without memantine treatment at baseline).[10]

Tables 3.20 to 3.23 show the results of these analyses for the MCI due to AD population who were not receiving symptomatic AD medication at baseline.[10]

Table 3.20: Change from baseline in CDR-SB at 18 months - MMRM, Clarity AD core study, MCI due to AD not treated with symptomatic AD medication at baseline subgroup

Statistic	Lecanemab (n=[redacted])	Placebo (n=[redacted])
Number of patients included in the MMRM	[redacted]	[redacted]
Number of subjects at 18-month visit (week 79)	[redacted]	[redacted]
Mean CDR-SB at baseline (SD)	[redacted]	[redacted]
Adjusted mean change from baseline at 18 months (SE)	[redacted]	[redacted]
Adjusted mean difference (lecanemab – placebo)	[redacted]	
95% CI for differences	[redacted]	
p-value	[redacted]	

Statistic	Lecanemab (n=[redacted])	Placebo (n=[redacted])
% Difference vs. placebo	[redacted]	

Based on Table 2, Response to clarification[10]
AD = Alzheimer's disease; CDR-SB = Clinical Dementia Rating - Sum of Boxes; CI = confidence interval; MCI = mild cognitive impairment; MMRM = mixed model for repeated measures; SD = standard deviation; SE = standard error

Table 3.21: Change from baseline in ADAS-Cog14 at 18 months – MMRM, Clarity AD core study, MCI due to AD without symptomatic AD medication at baseline subgroup

Statistic	Lecanemab (n=[redacted])	Placebo (n=[redacted])
Number of patients included in the MMRM	[redacted]	[redacted]
Number of subjects at 18-month visit (week 79)	[redacted]	[redacted]
Mean ADAS-Cog14 at baseline (SD)	[redacted]	[redacted]
Adjusted mean change from baseline at 18 months (SE)	[redacted]	[redacted]
Adjusted mean difference (lecanemab – placebo)	[redacted]	
95% CI for differences	[redacted]	
p-value	[redacted]	
% Difference vs. placebo	[redacted]	

Based on Table 3, Response to clarification[10]
ADAS-Cog14 = Alzheimer's Disease Assessment Scale - Cognitive subscale 14-item version; AD = Alzheimer's disease; CI = confidence interval; MCI = mild cognitive impairment; MMRM = mixed model for repeated measures; SD = standard deviation; SE = standard error

Table 3.22: Change from baseline in ADCOMS at 18 months – MMRM, Clarity AD core study, MCI due to AD without symptomatic AD medication at baseline subgroup

Statistic	Lecanemab (n=[redacted])	Placebo (n=[redacted])
Number of patients included in the MMRM	[redacted]	[redacted]
Number of subjects at 18-month visit (week 79)	[redacted]	[redacted]
Mean ADCOMS at baseline (SD)	[redacted]	[redacted]
Adjusted mean change from baseline at 18 months (SE)	[redacted]	[redacted]
Adjusted mean difference (lecanemab – placebo)	[redacted]	
95% confidence interval (CI) for differences	[redacted]	
p-value	[redacted]	
% Difference vs. placebo	[redacted]	

Based on Table 4, Response to clarification[10]
ADCOMS = Alzheimer's Disease Composite Score; AD = Alzheimer's disease; CI = confidence interval; MCI = mild cognitive impairment; MMRM = mixed model for repeated measures; SD = standard deviation; SE = standard error

Table 3.23: Change from baseline in ADCS-ADL-MCI at 18 months – MMRM, Clarity AD core study, MCI due to AD without symptomatic AD medication at baseline subgroup

Statistic	Lecanemab (n=[redacted])	Placebo (n=[redacted])

Number of patients included in the MMRM	[redacted]	[redacted]
Number of subjects at 18-month visit (week 79)	[redacted]	[redacted]
Mean ADCS-ADL-MCI at baseline (SD)	[redacted]	[redacted]
Adjusted mean change from baseline at 18 months (SE)	[redacted]	[redacted]
Adjusted mean difference (lecanemab – placebo)	[redacted]	
95% confidence interval (CI) for differences	[redacted]	
p-value	[redacted]	
% Difference vs. placebo	[redacted]	

Based on Table 5, Response to clarification[10]
ADCS-ADL-MCI = Alzheimer's Disease Cooperative Study-Activities of Daily Living Scale for Mild Cognitive Impairment; AD = Alzheimer's disease; CI = Confidence interval; MCI = mild cognitive impairment; MMRM = mixed model for repeated measures; SD = standard deviation; SE = Standard error

EAG comment: The EAG notes the company's statement that: *"These results in subgroups need to be interpreted with caution due to the small sample size and the slower clinical progression in MCI relative to mild AD."* However, the EAG considers that the results of the subgroup analyses raise a question about whether lecanemab has a clinically significant effect, in patients with MCI due to AD, when used in the context of UK SoC (i.e., without concomitant symptomatic AD treatment).

Tables 3.24 to 3.27 show the results of these analyses for the mild dementia due to AD population who were not receiving memantine at baseline.[10]

Table 3.24: Change from baseline in CDR-SB at 18 months - MMRM, Clarity AD core study, mild AD without memantine at baseline

Statistic	**Lecanemab ([redacted])**	**Placebo ([redacted])**
Number of patients included in the MMRM	[redacted]	[redacted]
Number of subjects at 18-month visit (week 79)	[redacted]	[redacted]
Mean at baseline (SD)	[redacted]	[redacted]
Adjusted mean at 18 months (SE)	[redacted]	[redacted]
Adjusted mean difference (lecanemab – placebo)	[redacted]	
95% confidence interval (CI) for differences	[redacted]	
p-value	[redacted]	
% Difference vs. placebo	[redacted]	

Based on Table 6, Response to clarification[10]
AD = Alzheimer's disease; CDR-SB = Clinical Dementia Rating-Sum of Boxes; CI = confidence interval; MCI = mild cognitive impairment; MMRM = mixed model for repeated measures; SD = standard deviation; SE = standard error

Table 3.25: Change from baseline in ADAS-Cog14 at 18 months – MMRM, Clarity AD core study, mild AD without memantine at baseline

Statistic	**Lecanemab ([redacted])**	**Placebo ([redacted])**
Number of patients included in the MMRM	[redacted]	[redacted]
Number of subjects at 18-month visit (week 79)	[redacted]	[redacted]
Mean at baseline (SD)	[redacted]	[redacted]

Adjusted mean at 18 months (SE)	[redacted]	[redacted]
Adjusted mean difference (lecanemab – placebo)	[redacted]	
95% confidence interval (CI) for differences	[redacted]	
p-value	[redacted]	
% Difference vs. placebo	[redacted]	

Based on Table 7, Response to clarification[10]
ADAS-Cog14 = Alzheimer's Disease Assessment Scale - Cognitive subscale 14-item version; AD = Alzheimer's disease; CI = confidence interval; MCI = mild cognitive impairment; MMRM = mixed model for repeated measures; SD = standard deviation; SE = standard error

Table 3.26: Change from baseline in ADCOMS at 18 months – MMRM, Clarity AD core study, mild AD without memantine at baseline

Statistic	**Lecanemab ([redacted])**	**Placebo ([redacted])**
Number of patients included in the MMRM	[redacted]	[redacted]
Number of subjects at 18-month visit (week 79)	[redacted]	[redacted]
Mean at baseline (SD)	[redacted]	[redacted]
Adjusted mean at 18 months (SE)	[redacted]	[redacted]
Adjusted mean difference (lecanemab – placebo)	[redacted]	
95% confidence interval (CI) for differences	[redacted]	
p-value	[redacted]	
% Difference vs. placebo	[redacted]	

Based on Table 8, Response to clarification[10]
ADCOMS = Alzheimer's Disease Composite Score; AD = Alzheimer's disease; CI = confidence interval; MCI = mild cognitive impairment; MMRM = mixed model for repeated measures; SD = standard deviation; SE = standard error

Table 3.27: Change from baseline in ADCS-ADL-MCI at 18 months – MMRM, Clarity AD core study, mild AD without memantine at baseline

Statistic	**Lecanemab ([redacted])**	**Placebo ([redacted])**
Number of patients included in the MMRM	[redacted]	[redacted]
Number of subjects at 18-month visit (week 79)	[redacted]	[redacted]
Mean at baseline (SD)	[redacted]	[redacted]
Adjusted mean at 18 months (SE)	[redacted]	[redacted]
Adjusted mean difference (lecanemab – placebo)	[redacted]	
95% confidence interval (CI) for differences	[redacted]	
p-value	[redacted]	
% Difference vs. placebo	[redacted]	

Based on Table 9, Response to clarification[10]
ADCS-ADL-MCI = Alzheimer's Disease Cooperative Study-Activities of Daily Living Scale for Mild Cognitive Impairment; AD = Alzheimer's disease; CI = confidence interval; MCI = mild cognitive impairment; MMRM = mixed model for repeated measures; SD = standard deviation; SE = standard error

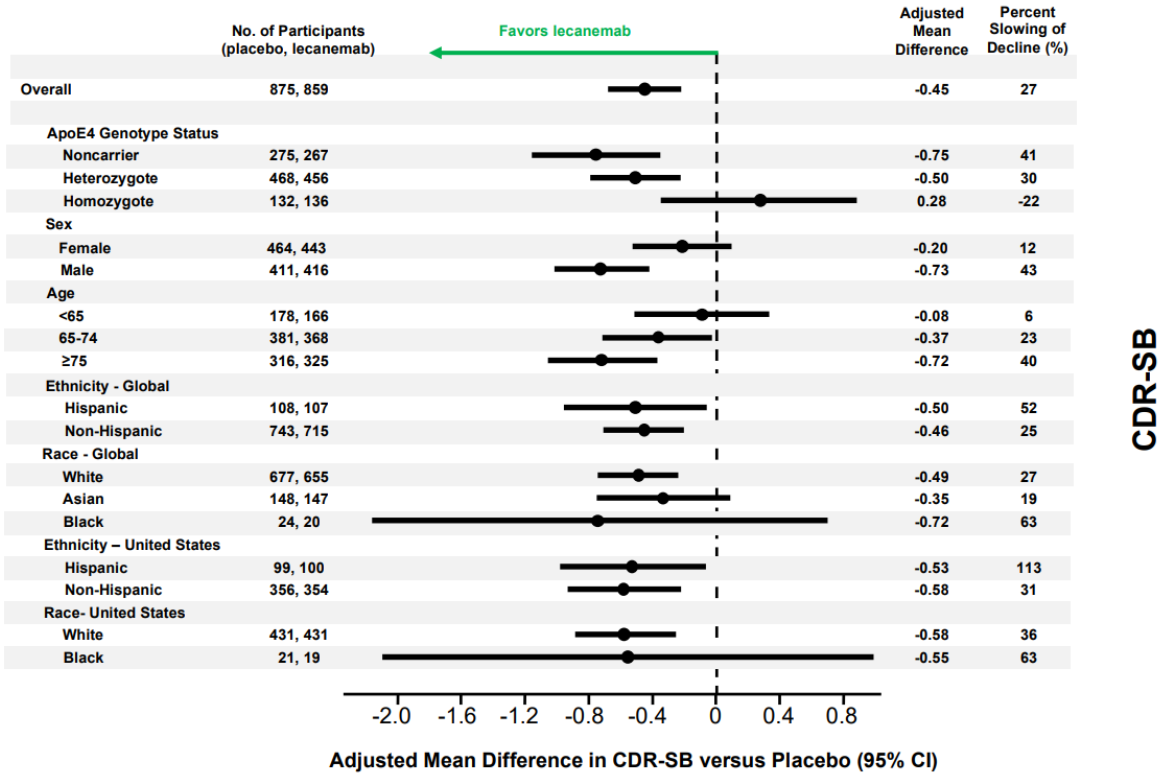
EAG comment: The EAG notes that for the population with mild dementia due to AD, the treatment effects of lecanemab appear to be consistent for the whole subgroup with mild dementia due to AD and

for those in whom SoC was more closely aligned with UK recommendations and clinical practice (i.e., not treated with memantine).

3.2.6.2 *ApoE4* genotype subgroup analyses

In the ITT FAS+ population, the majority of subjects were *ApoE4* carriers ([redacted]% of which [redacted]% were heterozygous *ApoE4* carriers and [redacted]% were homozygous *ApoE4* carriers, therefore greater variability of outcomes is expected in this smaller group due to reduced patient numbers). The remainder were *ApoE4* noncarriers ([redacted]%).[9] Subgroup analyses, by *ApoE4* genotype, showed a consistent pattern of reduced or absent lecanemab treatment effect across the four cognitive and functional outcome measures for the homozygous subgroup (CDR-SB, ADAS-Cog14, ADCOMS and ADCS MCI-ADL; Figures 3.14 to 3.17).[9]

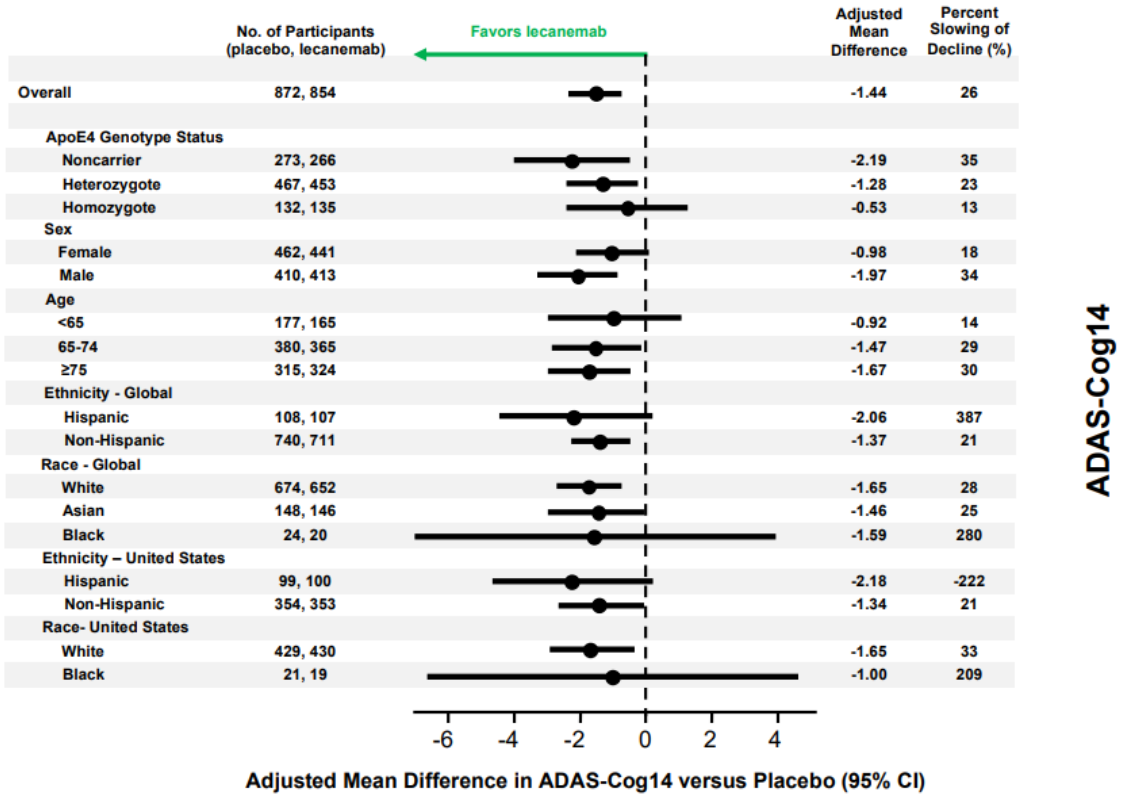
Figure 3.14: Subgroup analysis for adjusted mean difference in CDR-SB – ITT FAS+, intrinsic factors



Based on Figure 13, Appendix E of the CS[9]

ApoE4 = apolipoprotein E4; CDR-SB = Clinical Dementia Rating–Sum of Boxes; CI = confidence interval; FAS = full analysis set; ITT = intention-to-treat

Figure 3.15: Subgroup analysis for adjusted mean difference in ADAS-Cog14 – ITT FAS+, intrinsic factors



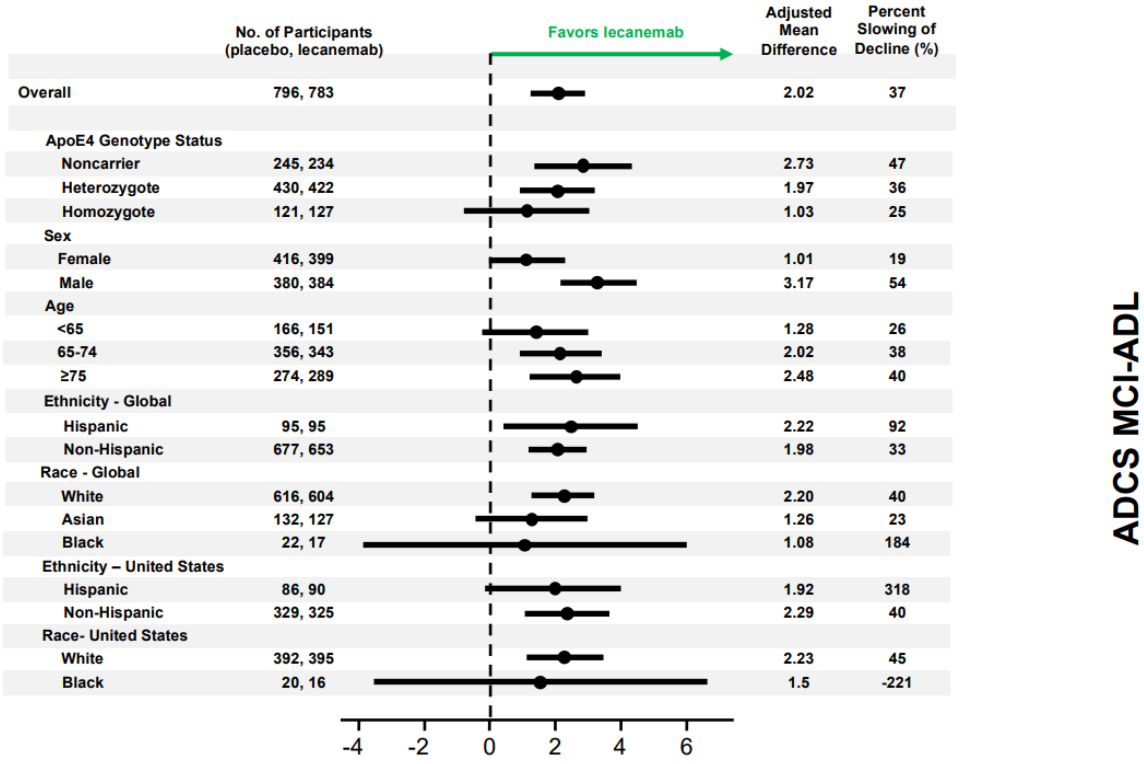
Based on Figure 14, Appendix E of the CS[9]
ApoE4 = apolipoprotein E4; ADAS-Cog14 = Alzheimer's Disease Assessment Scale - Cognitive Subscale with 14 tasks; CI = confidence interval; CS = company submission; FAS = full analysis set; ITT = intention-to-treat

Figure 3.16: Subgroup analysis for adjusted mean difference in ADCOMS – ITT FAS+, intrinsic factors

Based on Figure 15, Appendix E of the CS[9]

ADCOMS = Alzheimer's Disease Composite Score, *ApoE4* = apolipoprotein E4; CI = confidence interval; CS = company submission; FAS = full analysis set; ITT = intention-to-treat

Figure 3.17: Subgroup analysis for adjusted mean difference in ADCS MCI-ADL – ITT FAS+, intrinsic factors



Based on Figure 16, Appendix E of the CS[9]
ADCS MCI-ADL = Alzheimer's Disease Cooperative Study-Activities of Daily Living Scale for Mild Cognitive Impairment; *ApoE4* = apolipoprotein E4; CI = confidence interval; CS = company submission; FAS = full analysis set; ITT = intention-to-treat

In relation to the results of the *ApoE4* genotype subgroup analyses, the company stated:

[redacted]

[redacted]

Figure 3.18: Placebo CDR-SB by *ApoE4* genotype – ITT FAS+

[redacted]

Based on Figure 17, Appendix E of the CS[9]
ApoE4 = apolipoprotein E4, CDR-SB = Clinical Dementia Rating = Sum of Boxes; FAS = full analysis set; heter = *ApoE4* heterozygous; homo = *ApoE4* homozygous; ITT = intention-to-treat

EAG comment: The EAG considers that, whilst the above text and figure provide one possible explanation for the observed results of the *ApoE4* genotype subgroup analyses, it is also possible that treatment with lecanemab has a substantially smaller or no effect in the subgroup of patients who are *ApoE4* homozygous.

The EAG also notes that there appears to be a similarly consistent pattern (across the four cognitive and functional outcome measures CDR-SB, ADAS-Cog14, ADCOMS and ADCS-ADL-MCI) of decreasing lecanemab treatment effect with decreasing patient age.

3.2.7 Effectiveness results from Study 201

The company stated that Study 201 was not summarised in the CS (section B.2) because:[2]

- *"Clarity AD is the pivotal study supporting the marketing authorisation of lecanemab, whereas Study 201 was a Phase II dose-finding study.*
- *Study 201 had a different primary endpoint (ADCOMS) to Clarity AD (CDR-SB) and was not powered to detect differences between lecanemab and placebo in CDR-SB score.*

- *Only 161 patients in Study 201 were treated with 10 mg/kg biweekly lecanemab, of which [redacted] ([redacted]) completed study treatment. In contrast, 898 patients were treated with 10 mg/kg biweekly lecanemab in Clarity AD and 729 patients completed the core study."*

EAG comment: The EAG considers that results for the subgroup of participants Study 201 who received 10 mg/kg biweekly lecanemab are relevant to the decision problem. The EAG requested that full results be provided for this subgroup and that meta-analyses be conducted to combine data from this subgroup and data from Clarity AD.[13] The company provided the following results (Table 3.28) for Study 201:[10]

Table 3.28: Mean baseline and 18-month results for patients treated with lecanemab 10 mg/kg bi-weekly (Study 201, ITT FAS)

Statistic	Lecanemab 10 mg/kg bi-weekly, n				
	ADCOMS	ADAS-Cog14	MMSE	CDR-SB	FAQ
Number of patients included in the MMRM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
N (week 79)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Baseline mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
18-month mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean change from baseline in MMRM (SE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Least-squares mean difference (lecanemab – placebo)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
90% CI for differences	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
p-value	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Based on Based on Table 34, Response to clarification[10]
ADAS-Cog14 = Alzheimer's Disease Assessment Scale – Cognitive Subscale 14 item version; ADCOMS = Alzheimer's Disease Composite Score; CDR-SB = Clinical Dementia Rating-Sum of Boxes; CI = confidence interval; FAS = full analysis set; FAQ = Functional Assessment Questionnaire; ITT = intention-to-treat; kg = kilogram; mg =millgram; MMRM = mixed model for repeated measures; MMSE = mini-mental state examination; SD = standard deviation; SE = standard error

The company also provided information about concomitant use of symptomatic AD medication by participants in Study 201 (Table 3.29).[10]

Table 3.29: Concomitant use of symptomatic AD medications in Study 201 (SAS) AD by clinical subgroup (MCI and mild AD)

	Number of patients, n (%)			
	Lecanemab, 10 mg/kg bi-weekly (n=161)		Placebo (n=245)	
	MCI (n=96)	Mild AD (n=65)	MCI (n=158)	Mild AD (n=87)
Patients who received an AChEi	[redacted]	[redacted]	[redacted]	[redacted]
Patients who received memantine	[redacted]	[redacted]	[redacted]	[redacted]

	Number of patients, n (%)			
	Lecanemab, 10 mg/kg bi-weekly (n=161)		Placebo (n=245)	
	MCI (n=96)	Mild AD (n=65)	MCI (n=158)	Mild AD (n=87)
Patients who received an AChEi AND memantine	[redacted]	[redacted]	[redacted]	[redacted]
Patients who received a non-pharmacological intervention (e.g., cognitive training, cognitive stimulation, reminiscence therapy)	N/R	N/R	N/R	N/R
Patients who received a non-pharmacological intervention AND took an AChEi	N/R	N/R	N/R	N/R
Patients who received a non-pharmacological intervention AND took memantine	N/R	N/R	N/R	N/R
Patients who received a non-pharmacological intervention AND took both an AChEi and memantine	N/R	N/R	N/R	N/R

Based on Table 37, Response to clarification[10]
AChEi = acetylcholinesterase inhibitors; AD = Alzheimer's disease; MCI = mild cognitive impairment; N/R = not recorded; SAS = safety analysis set

As was the case for the Clarity AD study, the EAG questions whether the proportions of participants in Study 201 who were receiving concomitant symptomatic AD medications are likely to be consistent with current UK clinical practice.

3.2.8 Results of meta-analyses

The inverse-variance method recommended in the Cochrane Handbook[20] was used to pool the adjusted mean difference estimates from the MMRM in Clarity AD and Study 201, for CDR-SB, ADCOMS and ADAS-Cog14. The pooled estimate was calculated as:

$$\text{Generic inverse-variance weighted average} = \frac{\Sigma Y_i(\frac{1}{SE_i{}^2})}{\Sigma(\frac{1}{SE_i{}^2})}$$

where Y_i is the intervention effect estimated in the i^{th} study, SE_i is the standard error of that estimate, and the summation is across all studies. In this analysis, only two studies were considered, Clarity AD and Study 201, so the summation was across these two studies.

The adjusted mean differences from the MMRMs used in Clarity AD and Study 201 were used for the intervention effect estimate. Standard error was calculated using the confidence intervals using the following method:

$$\text{Standard error} = \frac{upper\ limit - lower\ limit}{x}$$

For 95% confidence intervals, x = 3.92, as was the case for Clarity AD, and for 90% confidence intervals, x = 3.29, as was the case for Study 201. This fixed-effect analysis is valid under the assumption that all estimates of treatment effect estimated the same underlying intervention effect. This assumption held since both Clarity AD and Study 201 investigated lecanemab 10 mg/kg biweekly.

Tables 3.30 and 3.31 show the treatment effects, confidence intervals and standard error used in the meta-analyses.

Table 3.30: Data from Clarity AD used in the meta-analysis – lecanemab (n=859) vs. placebo (n=875)

Outcome	Adjusted mean difference*	95% confidence interval	Standard error
CDR-SB	-0.451	-0.669, -0.233	0.111
ADCOMS	-0.05	-0.074, -0.027	0.012
ADAS-Cog14	-1.442	-2.270, -0.613	0.423

Based on Table 38, Response to clarification[10]
*Adjusted mean difference in change from baseline at 18 months [lecanemab – placebo]
AD = Alzheimer's disease; ADCOMS = Alzheimer's disease composite score; ADAS-Cog14 = Alzheimer's Disease Assessment Scale-Cognitive subscale; CDR-SB = Clinical Dementia Rating – Sum of Boxes

Table 3.31: Data from Study 201 used in the meta-analysis – lecanemab 10 mg/kg bi-weekly (n=152) vs. placebo (n=238)

Outcome	Adjusted mean difference*	90% confidence interval	Standard error
CDR-SB	-0.396	-0.821, 0.028	0.258
ADCOMS	-0.057	-0.102, -0.013	0.027
ADAS-Cog14	-2.313	-3.910, -0.717	0.971

Based on Table 39, Response to clarification[10]
*Adjusted mean difference in change from baseline at 18 months [lecanemab – placebo]
AD = Alzheimer's disease; ADCOMS = Alzheimer's disease composite score; ADAS-Cog14 = Alzheimer's Disease Assessment Scale-Cognitive subscale; CDR-SB = Clinical Dementia Rating – Sum of Boxes; kg = kilogram; mg = milligram

Table 3.32 shows the pooled estimates of adjusted mean difference for CDR-SB, ADCOMS, and ADAS-Cog14.

Table 3.32: Meta-analyses of common outcomes between Clarity AD and Study 201 (lecanemab 10 mg/kg biweekly vs. placebo)

Outcome	Adjusted mean difference *
CDR-SB	-0.442
ADCOMS	-0.051
ADAS-Cog14	-1.581

Based on Table 40, Response to clarification[10]
*Adjusted mean difference in change from baseline at 18 months [lecanemab – placebo]
AD = Alzheimer's disease; ADCOMS = Alzheimer's disease composite score; ADAS-Cog14 = Alzheimer's Disease Assessment Scale-Cognitive subscale; CDR-SB = Clinical Dementia Rating – Sum of Boxes; kg = kilogram; mg = milligram

EAG comment: The EAG notes that these meta-analyses resulted in similar point estimates for the treatment effects of lecanemab 10 mg/kg biweekly, to those obtained from the Clarity AD study (Tables 3.15 to 3.17)

3.2.9 Safety results of Clarity AD

3.2.9.1 AE overview

Treatment-emergent adverse events (TEAEs) were defined as an AE that emerged, re-emerged or worsened in severity relative to the pretreatment state during treatment or within 30 days following the last dose of study drug, having been absent at pretreatment.[2] Adverse events, except for infusion related reactions, were graded on a three-point scale of mild (discomfort noticed, but no disruption of normal daily activities), moderate (discomfort sufficient to reduce or affect normal daily activities) and severe (incapacitating, with inability to work or perform normal daily activities). Infusion related reactions were graded based on the Common Terminology Criteria for Adverse Events (CTCAE). Adverse events of special interest are presented in the Medical Dictionary for Regulatory Activities (MedDRA) Preferred Terms throughout the document.[2]

The company provide an initial overview where they describe rates of overall incidence of TEAEs was similar between lecanemab (798/898 [88.9%]) and placebo (735/897 [81.9%]); a summary of TEAEs is provided in Table 3.33. The most common TEAEs for patients receiving lecanemab including infusion related reactions ([redacted]%), ARIA-H (14.0%) and ARIA-E (12.6%), (Table 3.34).

EAG comment: The EAG notes that although the overall difference in the incidence of TEAEs, between the lecanemab and placebo groups, was small, the incidences of AE of special interest (ARIA-E, ARIA-H and infusion related reactions) were [redacted].

The company state, in their submission, that ARIA-E occurrences were monitored by early MRI and managed by dose interruption until resolution. The majority (81%) of ARIA-E cases resolved by four months since onset, with 7.9% of lecanemab and 0.7% of placebo patients experiencing interruption of study drug due to ARIA-E.[2] Infusion related reactions were largely mild to moderate (as per CTCAE grading), associated with the first dose, and could be managed with prophylactic treatment. In the lecanemab arm, only seven (0.8%) patients experienced a severe infusion-related reaction.[2]

The company also detail in their overview that the incidence of AEs leading to discontinuation of study treatment was [redacted]% and [redacted]% in the lecanemab and placebo arms, respectively (Table 68, Appendix O1.7). However, these data were actually derived from Table 69 of cited appendices. The CS stated that the difference is attributable to lower incidence of infusion related reaction (lecanemab: [redacted]%, placebo: [redacted]%), ARIA-H ([redacted]% versus [redacted]%), ARIA-E ([redacted]% versus [redacted]%), and superficial siderosis of the central nervous system ([redacted]% versus [redacted]%) in the placebo arm compared with the lecanemab arm. The incidence of TEAEs leading to study drug dose adjustment was [redacted]% and [redacted]% in the lecanemab and placebo arms, respectively.[9] The difference was attributed to management of infusion related reactions, ARIA-E, and ARIA-H, which were more common in patients treated with lecanemab.[2]

Noteworthy differences (>5%) between groups include the increased rates of overall treatment-related TEAEs, TEAEs leading to study drug dose adjustment, TEAEs leading to study drug dose interruption and TEAEs of special interest respectively. No differences (>5%) were reported for mortality or 'other SAEs' (serious adverse events).

EAG comment: The EAG notes that the incidence of TEAEs leading to the interruption or withdrawal of the study drug was [redacted].

Table 3.33: An overview of AEs (Clarity AD, SAS)

Category	Number of patients, n (%)	
	Lecanemab (n=898)	Placebo (n=897)
TEAEs	798 (88.9)	735 (81.9)
Treatment-related TEAEs[a]	401 (44.7)	197 (22.0)
Severe TEAEs	[redacted]	[redacted]
Serious TEAEs	126 (14.0)	101 (11.3)
Deaths[b]	6 (0.7)	7 (0.8)
Other SAEs[c]	[redacted]	[redacted]
Life threatening	[redacted]	[redacted]
Requires inpatient hospitalisation or prolongation of existing hospitalisation	[redacted]	[redacted]
Persistent or significant disability or incapacity	[redacted]	[redacted]
Congenital anomaly/birth defect	[redacted]	[redacted]
Important medical events	[redacted]	[redacted]
TEAEs leading to study drug dose adjustment	[redacted]	[redacted]
TEAEs leading to study drug withdrawal	[redacted]	[redacted]
TEAEs leading to study drug dose interruption	[redacted]	[redacted]
TEAEs leading to infusion interruption	[redacted]	[redacted]
TEAEs of special interest	[redacted]	[redacted]

Based on Adapted from Table 25, CS[2]

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

b) Includes all patients with SAE resulting in death.

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

AD = Alzheimer's disease; AE = adverse event; CS = company submission; MedDRA = Medical Dictionary for Regulatory Activities; n = number of patients in treatment group; SAE = serious adverse event; SAS = safety analysis set; TEAE = treatment-emergent adverse event

3.2.9.2 TEAEs >5%

The CS provides detail on all TEAEs that occurred in over 5% of patients in both the intervention and placebo groups. As can be observed in Table 3.34, TEAEs occurring in ≥5% of patients were broadly similar between lecanemab and placebo with the exception of infusion related reactions ([redacted]), ARIA-H microhaemorrhages and haemosiderin deposits (14% versus 7.7%) and ARIA-E (12.6% versus 1.7%) [redacted]. The CS clarifies that: *"Concurrent ARIA-E and ARIA-H, defined as overlapping in the AE duration of two ARIA events, occurred in 8.2% of lecanemab patients compared to 1.0% of placebo patients, however similar rates of isolated ARIA-H were observed between arms (lecanemab: 8.9%; placebo: 7.8%). In this table, ARIA-H is separated out into (1) ARIA-H cerebral microhaemorrhage and (2) superficial siderosis."*

Table 3.34: TEAEs reported in ≥5% of patients (Clarity AD, SAS)

MedDRA Preferred Term	Number of patients, n (%)	
	Lecanemab (n=898)	Placebo (n=897)
Patients with any TEAE	798 (88.9)	735 (81.9)
Infusion related reaction	[redacted]	[redacted]
ARIA-H microhaemorrhages and haemosiderin deposits	126 (14.0)	69 (7.7)
ARIA-E	113 (12.6)	15 (1.7)
Headache	100 (11.1)	73 (8.1)
Fall	93 (10.4)	86 (9.6)
Urinary tract infection	78 (8.7)	82 (9.1)
COVID-19	64 (7.1)	60 (6.7)
Back pain	60 (6.7)	52 (5.8)
Arthralgia	53 (5.9)	62 (6.9)
Superficial siderosis of central nervous system	50 (5.6)	22 (2.5)
Dizziness	49 (5.5)	46 (5.1)
Diarrhoea	48 (5.3)	58 (6.5)
Anxiety	45(5.0)	38 (4.2)

Based on Adapted from Table 26, CS[2]
AD = Alzheimer's disease; ARIA-E = amyloid-related imaging abnormality-oedema/effusion; ARIA-H = amyloid-related imaging abnormality-microhaemorrhage and haemosiderin deposit; COVID-19 = coronavirus disease of 2019; CS = company submission; MedDRA = Medical Dictionary for Regulatory Activities; n = number of patients in treatment group; SAS = safety analysis set; TEAE = treatment-emergent adverse event

The EAG noted that data did not describe or summarise treatment-emergent serious adverse events (TESAEs) and supply of this data was requested by type using MeDRA definitions. In their response to clarification, the company provided additional data breakdown by MedDRA system organ class and preferred term for the SAS in Clarity AD. These data are summarised below in Table 3.35.

3.2.9.3 Treatment-emergent SAEs

Treatment-emergent serious adverse events were broadly similar overall between groups (14% versus 11.3%) with all listed TESAEs occurring at a frequency of less <5% of groups. Injury, poisoning and procedural complications were the most common events reported with rates of [redacted] in the lecanemab group versus [redacted] in the placebo group respectively. Nervous system disorders were the second most common occurring event with rates of [redacted] in the lecanemab group versus [redacted] in the placebo group.

Table 3.35: Treatment-emergent serious adverse events by system organ class and preferred term (SAS)

MedDRA system organ class preferred term	Number of patients, n (%)	
	Lecanemab (N=898)	Placebo (N=897)
Subjects with any treatment-emergent serious adverse event	126 (14.0)	101 (11.3)
Nervous system disorders	[redacted]	[redacted]
Amyloid related imaging abnormality-microhaemorrhages and haemosiderin deposits	[redacted]	[redacted]
Amyloid related imaging abnormality-oedema/effusion	[redacted]	[redacted]
Cerebral haemorrhage	[redacted]	[redacted]
Haemorrhage intracranial	[redacted]	[redacted]
Blood and lymphatic system disorders	[redacted]	[redacted]
Cardiac disorders	[redacted]	[redacted]
Ear and labyrinth disorders	[redacted]	[redacted]
Eye disorders	[redacted]	[redacted]
Gastrointestinal disorders	[redacted]	[redacted]
General disorders and administration site conditions	[redacted]	[redacted]
Hepatobiliary disorders	[redacted]	[redacted]
Immune system disorders	[redacted]	[redacted]
Infections and infestations	[redacted]	[redacted]
Injury, poisoning and procedural complications	[redacted]	[redacted]
Investigations	[redacted]	[redacted]
Metabolism and nutrition disorders	[redacted]	[redacted]
Musculoskeletal and connective tissue disorders	[redacted]	[redacted]
Neoplasms benign, malignant and unspecified (including cysts and polyps)	[redacted]	[redacted]
Product issues	[redacted]	[redacted]
Psychiatric disorders	[redacted]	[redacted]
Renal and urinary disorders	[redacted]	[redacted]
Reproductive system and breast disorders	[redacted]	[redacted]
Respiratory, thoracic and mediastinal disorders	[redacted]	[redacted]
Skin and subcutaneous tissue disorders	[redacted]	[redacted]
Social circumstances	[redacted]	[redacted]
Vascular disorders	[redacted]	[redacted]

Based on Adapted from Table 41, clarification response[10]
MedDRA = Medical Dictionary for Regulatory Activities; SAS = safety analysis set

3.2.9.4 AEs of special interest

The CS reports that the lecanemab group experienced a [redacted] of any TEAEs of special interest compared to placebo ([redacted]). The most common event type in the lecanemab group were infusion-related reactions (26.4%), while the most common event type in the placebo group was ARIA-H related events at [redacted]. Infusion-related reactions (26.4% versus 7.4%), skin rash

([redacted]), other hypersensitivity reactions ([redacted]), ARIA-E ([redacted]), and ARIA-H ([redacted]) were [redacted] (Table 3.36). The CS noted that most (lecanemab [redacted]; placebo [redacted]) AEs of special interest were considered treatment-related,[2] citing Table 16.3.2.6.2 from the CSR (this table was not included in the submitted CSR files). [redacted][6]

Table 3.36: TEAEs Treatment-emergent adverse events of special interest

Preferred term	Number of patients, n (%)	
	Lecanemab (n=898)	Placebo (n=897)
Patients with any TEAE of special interest	[redacted]	[redacted]
ARIA-E	113 (12.6)	15 (1.7)
ARIA-H	155 (17.3)	81 (9.0)
Macrohaemorrhage	5 (0.6)	1 (0.1)
Superficial siderosis	50 (5.6)	21 (2.3)
Cerebral microhaemorrhage	126 (14.0)	68 (7.6)
Infusion-related reactions	237 (26.4)	66 (7.4)
Skin rash	[redacted]	[redacted]
Other hypersensitivity	[redacted]	[redacted]
Suicidal behaviour	[redacted]	[redacted]
Suicidal ideation	[redacted]	[redacted]

Based on Adapted from table 27, CS[2]
ARIA-E = amyloid-related imaging abnormality-oedema/effusion; ARIA-H = amyloid-related imaging abnormality-microhaemorrhage and haemosiderin deposit; n = number of patients in treatment group; SAS = Safety Analysis Set; TEAE = treatment-emergent adverse events

EAG comment: The EAG notes that, considering data from the Clarity AD CSR (Table 3.37)[7] which were not included in the company's summary of AEs of special interest, it is clear that most ARIA occurred in study participants who were *ApoE4* gene carriers, with the highest incidence being in *ApoE4* homozygous carriers.

Table 3.37: Summary of treatment-emergent ARIA-E and ARIA-H by *ApoE4* genotype

ARIA term	Number of patients, n/n (%)	
	Lecanemab (n=898)	Placebo (n=897)
ARIA-E	[redacted]	[redacted]
ApoE4 non-carriers	[redacted]	[redacted]
ApoE4 carriers	[redacted]	[redacted]
ApoE4 heterozygous carriers	[redacted]	[redacted]
ApoE4 homozygous carriers	[redacted]	[redacted]
ARIA-H	[redacted]	[redacted]

ARIA term	Number of patients, n/n (%)	
	Lecanemab (n=898)	Placebo (n=897)
ApoE4 non-carriers	[redacted]	[redacted]
ApoE4 carriers	[redacted]	[redacted]
ApoE4 heterozygous carriers	[redacted]	[redacted]
ApoE4 homozygous carriers	[redacted]	[redacted]

Based on Table 14.3.2.6.10, CSR[7]
ApoE4 = apolipoprotein E4; ARIA-E = amyloid-related imaging abnormality – oedema/effusion; ARIA-H = amyloid-related imaging abnormality – haemorrhage

The following additional data, on *ApoE4* genotype and risk of ARIA, was reported in the draft SmPC: [redacted][6]

3.2.9.4.1 ARIA-E

The overall incidence of ARIA-E was 12.6% for lecanemab, compared to 1.7% for placebo (Table 3.38). The CS states that "*all ARIA-E events were considered treatment-related TEAEs, and the incidence of serious ARIA-E was* [redacted] *in the lecanemab arm; there were* [redacted] *in the placebo arm*." With respect to radiographic severity, the incidence of moderate and severe ARIA-E was [redacted]. Incidence of asymptomatic ARIA-E was also [redacted].

Table 3.38: Treatment-emergent ARIA-E by maximum radiographic severity

ARIA term Maximum radiographic severity	Number of patients, n (%)	
	Lecanemab (n=898)	Placebo (n=897)
Any ARIA-E	113 (12.6)	15 (1.7))
Mild	[redacted]	[redacted]
Moderate	[redacted]	[redacted]
Severe	[redacted]	[redacted]
Missing	[redacted]	[redacted]
Symptomatic ARIA-E	25 (2.8)	0 (0.0)
Asymptomatic ARIA-E	88 (9.8)	15 (1.7)

Based on Table 28, CS[2]
ARIA-E = amyloid-related imaging abnormality – oedema/effusion; n = number of patients in treatment group; SAS = safety analysis set

The CS states that *"ARIA-E events in the placebo arm were randomly distributed over the course of treatment. For the first episode, most cases of treatment-emergent ARIA-E in the lecanemab arm occurred within the first 3 months of treatment ([redacted]) (Table 67, Appendix O1.8)."*

Table 3.39: Time to onset of treatment-emergent ARIA-E (Clarity AD, SAS)

Time to onset of treatment-emergent ARIA-E	Number of patients n (%)*	
	Lecanemab (n=898)	Placebo (n=897)
Subjects with first ARIA-E	113	15
≤13 weeks visit	[redacted]	[redacted]
>13 to ≤27 weeks visit	[redacted]	[redacted]
>27 to ≤39 weeks visit	[redacted]	[redacted]
>39 to ≤53 weeks visit	[redacted]	[redacted]
>53 to ≤65 weeks visit	[redacted]	[redacted]
>65 weeks visit	[redacted]	[redacted]

Based on Adapted from Table 70, CS appendices[9]
* Percentage based on patients with ARIA-E.
Based on scheduled visit for safety MRI and a visit window of ±8 days is allowed for each visit.
AD = Alzheimer's disease; ARIA-E = amyloid-related imaging abnormality – oedema/effusion; CS = company submission; n = number of patients in treatment group; SAS = safety analysis set

It is also stated that "*Most patients in both treatment arms experienced ARIA-E without recurrence, with [redacted] lecanemab patients and [redacted] of placebo patients experiencing a second ARIA-E event. [redacted] lecanemab patients and [redacted] placebo patients experienced a third occurrence. [redacted] lecanemab patient experienced 4 episodes of ARIA-E…Resolution is defined by resolution of both radiographic and clinical signs and symptoms of ARIA-E. The majority of ARIA-E resolved by four months since first onset in both treatment arms (lecanemab: [redacted]; placebo: [redacted]). All 113 cases of first ARIA-E events in the lecanemab group were resolved. In the placebo group, of the 15 cases of first ARIA-E, 12 resolved and 3 remained ongoing (Table 67, Appendix O1.8)".* [2, 9]

3.2.9.4.2 ARIA-H

Amyloid-related imaging abnormality-microhaemorrhage and haemosiderin deposit is comprised of three subcategories; macrohaemorrhage, superficial siderosis, and cerebral microhaemorrhage and can occur as 1) isolated ARIA-H events not associated with ARIA-E and 2) concurrent with ARIA-E (i.e., having both ARIA-H and ARIA-E at the same time).[2] Data are presented in the CS for overall, isolated and concurrent ARIA-H.

The incidence of ARIA-H was higher in the lecanemab arm (155/898 [17.3%]) compared to the placebo arm (81/897 [9.0%]).[2] The incidence of serious ARIA-H was [redacted]) in the lecanemab arm and [redacted]) in the placebo arm.[2] The EAG highlighted that treatment emergent ARIA-H by *APoE4* status was not presented in the company's summary of adverse events of special interest, but it is clear that [redacted] ARIA-H occurred in study participants who were *ApoE4* gene carriers, with [redacted] being in *ApoE4* homozygous carriers. Stratification of treatment emergent ARIA-H by *APoE4* status is described above in Table 3.37.

Most treatment-emergent ARIA–H, in both the lecanemab and placebo groups, were radiographically mild (lecanemab: [redacted]]; placebo [redacted] to moderate (lecanemab: [redacted]]; placebo [redacted].[2] The incidence of severe ARIA-H was [redacted] in the

lecanemab group and [redacted] in the placebo group. Table 3.40 provides a breakdown of ARIA-H by radiographic severity. The CS also states that *"most cases of ARIA-H was asymptomatic (lecanemab: [redacted]; placebo [redacted] and balanced across ARIA-H subcategories…"*[2]

Table 3.40: Treatment-emergent ARIA-H by maximum radiographic severity (Clarity AD, SAS)

Maximum radiographic severity	Number of patients, n (%)	
	Lecanemab (n=898)	Placebo (n=897)
Subjects with ARIA-H	155 (17.3)	81 (9.0)
Mild	[redacted]	[redacted]
Moderate	[redacted]	[redacted]
Severe	[redacted]	[redacted]
Missing	[redacted]	[redacted]

Based on Adapted from Table 29, CS[2]
AD = Alzheimer's disease; ARIA-H = amyloid-related imaging abnormality-microhaemorrhage and haemosiderin deposit; CS = company submission; n = number of patients in treatment group; SAS = safety analysis set

The CS states that *"most cases of ARIA-H in both treatments arms were ongoing at the end of the Core Study. All cases of microhaemorrhage with lecanemab or placebo were ongoing, which was expected…"*[2] Similar trends were observed in all ARIA-H subcategories. Table 3.41 indicates the time to onset of ARIA-H. Most events occurred prior to the 13-week visit, in both groups, with an increased frequency in the lecanemab group compared to placebo ([redacted]). During the time period >13 to ≤27 weeks, there were also increased rates of ARIA-H in the lecanemab group ([redacted]) versus the placebo group ([redacted]).[2] Events rates were [redacted], during the >27 to ≤39 week and >53 to ≤65 week time periods, and were [redacted] during the >39 to ≤53 week time period and again after the 65 weeks visit.[2]

Table 3.41: Time to onset of treatment-emergent ARIA-H (Clarity AD, SAS)

Time to onset of treatment-emergent ARIA-H	Number of patients	
	Lecanemab (n=898)	Placebo (n=897)
Total number of ARIA-H events	[redacted], n (%)*	[redacted], n (%)*
≤13 weeks visit	[redacted]	[redacted]
>13 to ≤27 weeks visit	[redacted]	[redacted]
>27 to ≤39 weeks visit	[redacted]	[redacted]
>39 to ≤53 weeks visit	[redacted]	[redacted]
>53 to ≤65 weeks visit	[redacted]	[redacted]
>65 weeks visit	[redacted]	[redacted]

Based on Adapted from Table 30, CS[2]
* Percentage based on patients with ARIA-H. Based on scheduled visit for safety MRI and a visit window of ±8 days is allowed for each visit.
AD = Alzheimer's disease; ARIA-H = amyloid-related imaging abnormality-microhaemorrhage and haemosiderin deposit; CS = company submission; n = number of patients in treatment group; SAS = safety analysis set

Isolated ARIA-H events were similar between groups, overall and by maximum radiographic severity, (Table 3.42). The CS clarifies that *"isolated ARIA-H events occur throughout the course of treatment in both treatment arms"* and that *"Rates of symptomatic isolated ARIA-H were similar between lecanemab ([redacted]) and placebo ([redacted])."*

Table 3.42: Treatment-emergent isolated ARIA-H by maximum radiographic severity

Maximum radiographic severity	Number of patients, n (%)	
	Lecanemab (n=898)	Placebo (n=897)
Subjects with ARIA-H	80 (8.9)	70 (7.8)
Mild	[redacted]	[redacted]
Moderate	[redacted]	[redacted]
Severe	[redacted]	[redacted]
Missing	[redacted]	[redacted]

Based on Adapted from Table 31, CS[2]
ARIA-H = amyloid-related imaging abnormality-microhaemorrhage and haemosiderin deposit; CS = company submission; n = number of patients in treatment group; SAS = safety analysis set

Overall rates of concurrent ARIA-E and ARIA-H (Table 3.43) were increased in the lecanemab arm (74/898 [8.2%]) compared to placebo (9/897 [1.0%]).[2] The CS states that the onset time, distributions, and symptoms of concurrent ARIA-E and ARIA-H follow the pattern of ARIA-E and opines that the excess incidence of ARIA-H in the lecanemab arm is most likely due to ARIA-H that occurs during the onset or resolution of ARIA-E.[2]

Table 3.43: Treatment-emergent concurrent ARIA-H by maximum radiographic severity

Maximum radiographic severity	Number of patients, n (%)	
	Lecanemab (n=898)	Placebo (n=897)
Subjects with ARIA-H	74 (8.2)	9 (1.0)
Mild	[redacted]	[redacted]
Moderate	[redacted]	[redacted]
Severe	[redacted]	[redacted]
Missing	[redacted]	[redacted]

Based on Adapted from Table 32, CS[2]
ARIA-H = amyloid-related imaging abnormality-microhaemorrhage and haemosiderin deposit; CS = company submission; n = number of patients in treatment group; SAS = safety analysis set

3.2.9.4.3 Infusion-related reactions

Infusion-related reactions, occurred in 26.4% of patients in the lecanemab group compared to 7.4% of patients in the placebo group.[2] Grade 1 and 2 reactions were most common in both groups grade 1 (lecanemab: [redacted]; placebo: [redacted]) and grade 2 (lecanemab: [redacted]; placebo: [redacted]). [redacted] in the placebo arm reported Grade 3 or 4 infusion-related reactions. In the lecanemab arm, [redacted] and [redacted] patients reported grade 3 and grade 4 infusion-related reactions, respectively, The CS clarified that, as per Clarity AD protocol, all [redacted] patients who experienced a grade 3 or 4 reaction were discontinued from study treatment and did not receive subsequent infusions.[2]

Table 3.44: Summary of infusion-related reactions by maximum grade (Clarity AD, SAS)

NCI-CTCAE Grade	Number of patients, n (%)	
	Lecanemab (n=898)	Placebo (n=897)
Any grade	237 (26.4)	66 (7.4)
Grade 1	[redacted]	[redacted]
Grade 2	[redacted]	[redacted]
Grade 3	[redacted]	[redacted]
Grade 4	[redacted]	[redacted]
Grade 5	[redacted]	[redacted]
Missing	[redacted]	[redacted]

Based on Adapted from Table 33, CS[2]
CTCAE = Common Terminology Criteria for Adverse Events; SAS = safety analysis set

The CS states that *"Most patients who experienced an infusion-related reaction continued to the next visit (lecanemab:* [redacted] *; placebo* [redacted] *; of which* [redacted] *lecanemab patients and* [redacted] *placebo patients received at least one preventative medication (nonsteroidal anti-inflammatory drugs [NSAIDs], antihistamines and glucocorticoids) prior to subsequent infusions. Of these,* [redacted] *lecanemab patients and* [redacted] *) placebo patients did not have subsequent infusion-related reactions.' It further describes that 'Out of the* [redacted] *lecanemab and* [redacted] *placebo patients who experienced an infusion-related reaction but did not receive a preventative medication prior to subsequent infusions,* [redacted] *and* [redacted] *patients did not have a subsequent infusion-related reaction, respectively."*[2]

3.2.9.4.4 Intracerebral haemorrhage

The draft SmPC for lecanemab notes that [redacted][6]

3.2.9.5 Mortality

Similar rates of TEAEs leading to death occurred in the lecanemab (6/898 [0.7%]) and placebo (7/897 [0.8%]) groups (Table 3.45).[9]

The CS states that there were no deaths related to lecanemab and no deaths due to treatment-emergent ARIA. Further detail is provided that *"There were 13 treatment-emergent deaths, and 2 deaths were nontreatment-emergent (i.e. occurred >30 days after the last study treatment administration). One nontreatment-emergent death occurred in the lecanemab arm 36 days after the last dose of lecanemab. The death was due to diabetic ketoacidosis and was not considered to be related to lecanemab treatment. One nontreatment-emergent death due to cardio-respiratory arrest occurred in the placebo arm 49 days after the last dose."*[9]

The CS states that *"a similar proportion of deaths occurred in the lecanemab (* [redacted] *) and placebo (i.e. newly treated core study placebo subjects) (* [redacted] *) groups in the Clarity AD OLE study. Both of the deaths in the lecanemab group occurred in patients with significant comorbidities and risk factors including anticoagulation, which are thought to have contributed to macrohaemorrhage or death."*[9]

Interim results of the OLE (data cut off; December 1, 2022) (which included the core study) for mortality with concurrent cerebral macrohaemorrhage and anticoagulant use can be seen in Table 3.46. The CS[9] stated that deaths with concurrent cerebral macrohaemorrhage and anticoagulant use, in the lecanemab group, *"occurred in the OLE and had significant comorbidities and risk factors including anticoagulation which are thought to have contributed to macrohaemorrhage or death."* The rate of macrohaemorrhages for patients on both anticoagulants and lecanemab was [redacted] in the core study and [redacted] across the core phase and in the OLE.[9]

Information provided in the response to clarification[10] included mortality data for the OLE. Overall, 15 treatment-emergent deaths occurred, six in the core study with lecanemab treatment and nine additional deaths in the OLE.

The response noted that AEs leading to death in the extension phase were myocardial infarction, COVID-19 pneumonia, COVID-19, cerebral haemorrhage, possible seizure and cerebrovascular accident, acute multifocal intracerebral haemorrhage post tissue plasminogen activator, road traffic accident, and cardiac failure acute.

Table 3.45: Summary of treatment-emergent deaths (Clarity AD, SAS)

MedDRA system organ class preferred term	Number of patients, n (%)	
	Lecanemab (n=898)	Placebo (n=897)
Subjects with any TEAE leading to death	6 (0.7)	7 (0.8)
Cardiac disorders	[redacted]	[redacted]
Myocardial infarction	[redacted]	[redacted]
General disorders and administration site conditions	[redacted]	[redacted]
Death	[redacted]	[redacted]
Infections and infestations	[redacted]	[redacted]
COVID-19	[redacted]	[redacted]
Neoplasms benign, malignant, and unspecified (including cysts and polyps)	[redacted]	[redacted]
Metastases to bone	[redacted]	[redacted]
Metastases to meninges	[redacted]	[redacted]
Pancreatic carcinoma	[redacted]	[redacted]
Nervous system disorders	[redacted]	[redacted]
Cerebrovascular accident	[redacted]	[redacted]
Haemorrhage intracranial	[redacted]	[redacted]
Respiratory, thoracic, and mediastinal disorders	[redacted]	[redacted]
Acute respiratory failure	[redacted]	[redacted]
Respiratory failure	[redacted]	[redacted]

Based on Adapted from Table 34, CS [2]
Non-treatment-emergent deaths not included.
AD = Alzheimer's disease; MedDRA = Medical Dictionary for Regulatory Activities; COVID-19 = coronavirus disease 2019; CS = company submission; n = number of patients in treatment group; SAS = safety analysis set; TEAE = treatment-emergent adverse events

Table 3.46: Deaths with concurrent cerebral macrohaemorrhage and anticoagulant use

Study	Total		Anticoagulant	
	Placebo (n=897)	Lecanemab (n=1608)	Placebo (n=74)	Lecanemab (n=140)
Clarity AD Core & OLE Deaths with concurrent macrohaemorrhage, %	[redacted]	[redacted]	[redacted]	[redacted]
Based on Adapted from Table 30, CS Appendices[9] AD = Alzheimer's disease; CS = company submission; OLE = Open-label extension				

3.2.9.6 OLE interim safety data

The EAG sought clarification on safety data that are available from the OLE and requested that if available, these data could be provided. The Company in response to this request provided additional data.

In their response, the company state that *"Safety data from the OLE are available for 1,612 patients at the interim data cut off on 1st December 2022. This Safety Analysis Set consists of* [redacted] *treated with lecanemab in the core study, and* [redacted] *treated with placebo in the core study who then crossed over to lecanemab in the OLE. Patients who received placebo in the core study and did not enter the OLE are not included. Safety data are only reported for the entire Safety Analysis Set, hence are not stratified according to treatment arm allocation in the core study."*[10]

The mean duration of exposure to lecanemab in the OLE was [redacted] months (range: [redacted]).[10]

Of the 1,612 patients in the OLE SAS, [redacted]) had at least one TEAE, the majority of which were mild or moderate and nonserious. This rate of TEAEs was lower than that seen in the lecanemab arm of the core study ([redacted]) and higher than that seen in the placebo arm of the core study ([redacted]). Severe TEAEs were reported for [redacted]) patients.[10] Table 3.47 provides a summary of TEAEs that occurred during the OLE.

Table 3.47: Overview of TEAEs – lecanemab treated period (Clarity AD OLE, SAS)

Category	Lecanemab (N=1,612), n (%)
TEAEs	[redacted]
Treatment-related TEAEs[a]	[redacted]
Severe TEAEs	[redacted]
Serious TEAEs	[redacted]
Deaths[b]	[redacted]
Other SAEs[c]	[redacted]
Life threatening	[redacted]
Requires inpatient hospitalisation or prolongation of existing hospitalisation	[redacted]
Persistent or significant disability or incapacity	[redacted]
Congenital anomaly/birth defect	[redacted]
Important medical events	[redacted]
TEAEs leading to study drug dose adjustment	[redacted]
TEAEs leading to study drug withdrawal	[redacted]

Category	Lecanemab (N=1,612), n (%)
TEAEs leading to study drug dose interruption	[redacted]
TEAEs leading to infusion interruption	[redacted]
TEAEs of special interest	[redacted]

Based on Table 43, clarification response.[10]
a) Includes TEAEs considered by the Investigator to be related to study drug or TEAEs with missing causality.
b) Includes all subjects with SAE resulting in death.
c) Includes subjects with nonfatal SAEs only. If a subject had both fatal and nonfatal SAEs, the subject is counted in the fatal row and is not counted in the nonfatal row
AD = Alzheimer's disease; OLE = open-label extension; SAE = serious adverse event; SAS = safety analysis set; TEAE = treatment emergent adverse event

The most common events overall were infusion related reactions ([redacted]), ARIA-H cerebral microhaemorrhage ([redacted]), COVID-19 ([redacted]), and ARIA-E ([redacted]), which is consistent with the core study.[10]

Data describing TEAEs occurring in ≥5% reported during the OLE were also provided. The most common events overall were infusion related reactions ([redacted]), ARIA-H cerebral microhaemorrhage ([redacted]), COVID-19 ([redacted]), and ARIA-E ([redacted]), which is consistent with the core study. TEAEs of infusion-related reactions and ARIA-E occurred at a lower rate in the OLE compared to lecanemab in the core study. Excluding infusion-related reactions and ARIA, TEAEs occurring in ≥5% of subjects were lower in the OLE compared to lecanemab in the core study.[10]

Table 3.48: Treatment-emergent AEs reported in ≥5% of patients (Clarity AD OLE, SAS)

MedDRA Preferred Term	Lecanemab (N=1,612), n (%)
Subjects with any TEAE	[redacted]
Infusion related reaction	[redacted]
Amyloid related imaging abnormality-microhaemorrhages and haemosiderin deposits	[redacted]
COVID-19	[redacted]
Amyloid related imaging abnormality-oedema/effusion	[redacted]
Headache	[redacted]
Fall	[redacted]
Urinary tract infection	[redacted]
Back pain	[redacted]
Superficial siderosis of central nervous system	[redacted]
Arthralgia	[redacted]
Dizziness	[redacted]

Based on Table 44, clarification response[10]
AD = Alzheimer's disease; AE = adverse event; COVID-19 = coronavirus disease 2019; MedDRA = Medical Dictionary for Regulatory Activities; OLE = Open-label extension; SAS = safety analysis set; TEAE = treatment-emergent adverse event

The overall incidence of adverse events of special interest (ARIA-E, ARIA-H and infusion-related reactions) was similar in the OLE SAS to the lecanemab arm of the core study ([redacted] versus

[redacted], respectively).[10] Table 3.49 provides a summary of TEAEs of special interest that occurred during the OLE.

Table 3.49: Treatment-emergent adverse events of special interest (Clarity AD OLE, safety population)

Preferred term	Lecanemab (n=1,612) n (%)
Subjects with any TEAE of special interest	[redacted]
ARIA-E	[redacted]
ARIA-H	[redacted]
Macrohaemorrhage	[redacted]
Superficial siderosis	[redacted]
Cerebral microhaemorrhage	[redacted]
Infusion-related reactions	[redacted]
Skin rash	[redacted]
Other hypersensitivity	[redacted]
Suicidal behaviour	[redacted]
Suicidal ideation	[redacted]

Based on Table 45, clarification response[10]
AD = Alzheimer's disease; ARIA-E = amyloid-related imaging abnormality-oedema/effusion; ARIA-H = amyloid-related imaging abnormality-microhaemorrhage and haemosiderin deposit; n = number of subjects in treatment group; OLE = open-label extension; TEAE = treatment-emergent adverse events

3.3 Critique of trials identified and included in the indirect comparison and/or multiple treatment comparison

Not applicable (see Section 3.4).

3.4 Critique of the indirect comparison and/or multiple treatment comparison

The CS (Section B.2.9) states that: *"An indirect treatment comparison was not conducted as Clarity AD provides direct evidence for the comparison of interest."*[2]

3.5 Additional work on clinical effectiveness undertaken by the EAG

Not applicable.

3.6 Conclusions of the clinical effectiveness section

The CS and response to clarification provided sufficient details for the EAG to appraise the literature searches conducted to identify relevant clinical evidence for the efficacy and safety of existing treatments for AD. Searches conducted in August 2023 were transparent and reproducible. A good range of databases and conference proceedings were searched. In addition to the clinical effectiveness search, the company also conducted a second set of searches to identify available evidence on the natural history of patients with early AD. The primary objective of this SLR was to identify and summarise the evidence describing the probability of natural disease progression from MCI into AD. Overall, the EAG has no major concerns about the literature searches conducted, however separate adverse events searches may have retrieved additional relevant studies.

The Clarity AD trial and Study 201 both provided direct comparisons of lecanemab plus established clinical management versus established clinical management. The CS,[2] focused on Clarity AD and did not initially include clinical effectiveness results from Study 201 or any pooled treatment effects for

these two studies. However, the summary of results from Study 201 and meta-analyses, provided in response to clarification questions,[10] indicated that treatment effects were similar across the two studies and hence the pooled treatment effects did not differ substantially from the results of Clarity AD.

The population in the key clinical trial, Clarity AD, and of those eligible for lecanemab was narrower than that specified in the NICE final scope,[3] in that the inclusion criteria for Clarity AD required confirmation of the presence of amyloid beta (Aβ) pathology using either a CSF amyloid protein test or amyloid PET scan; the definition of the population used in the NICE final scope does not specify confirmatory testing, although the economic analysis section of the scope does state *"the use of lecanemab is conditional on the presence of amyloid pathology,"* and the SmPC for lecanemab states that:
"[redacted]."[9] Confirmation of Aβ pathology is key to the use of lecanemab treatment because lecanemab is an anti-Aβ disease modifying treatment (DMT); it is a humanised monoclonal antibody, the mechanism of action of which is to bind aggregated Aβ peptides, marking them for clearance by the immune system. As noted in the CS, this testing is not routinely used in the NHS to diagnose AD.[2] Therefore, there are consequences of this testing that need to be valued to assess the effectiveness and cost effectiveness of lecanemab.[4] These include the cost of testing and any potential harms to health of those tested, who include more patients than those who turn out to be eligible for lecanemab. Indeed, the potential harm of lumbar puncture (for the CSF biomarker test) and PET scan are recognised in the NICE guideline:[5]

"The committee discussed the potentially stressful and unpleasant diagnostic tests that could be used in a specialist setting. These include lumbar puncture to obtain cerebrospinal fluid (CSF) for biomarker tests, MRI and other imaging tests. These tests may not be well tolerated by all patients, particularly those with claustrophobia (MRI) or people with more severe dementia. The committee noted that it was important to use these tests only if they are required to reduce diagnostic uncertainty, if the person with suspected dementia/with dementia requiring subtype diagnosis agrees and if they can comply with test requirements. The committee agreed that to avoid unnecessary tests being undertaken, it was important to include a specific recommendation stating these tests only be undertaken if they would reduce diagnostic uncertainty and reducing that uncertainty would change management."

The EAG considers that the evidence presented indicates that, overall, for patients who had MCI due to AD or mild dementia due to AD and confirmed Aβ pathology, treatment with lecanemab was consistently associated with statistically significant reductions in decline, across a variety of measures of cognition and function, compared to placebo at 18-months. However, the EAG considers that both the long-term (beyond 18-months) effects and the clinical significance of the observed treatment effects of lecanemab are uncertain. There was also some evidence to indicate that (over 18 months) the rates of progression to moderate and severe AD were lower in patients treated with lecanemab than placebo; for patients who had MCI due to AD the rates of progression to moderate or severe AD over 18 months were [redacted] in the lecanemab treated group and [redacted] in the placebo group, calculated odds ratio (OR) [redacted], and for patients who had mild AD the rates of progression to moderate or severe AD over 18 months were [redacted] in the lecanemab treated group and [redacted] in the placebo group, calculated OR [redacted].

The results of subgroup analyses from the Clarity AD trial, presented in Appendix E of the CS,[9] indicate that there may be some patient groups for whom the efficacy of lecanemab (with respect to reduction in decline in cognition and function at 18 months) is also uncertain (e.g., homozygous *ApoE4* carriers and younger [<65 years of age] patients). This is particularly notable for the homozygous *ApoE4* carrier

population, where the adjusted mean difference in change from baseline in CDR-SB was 0.28 (22% faster decline, confidence interval including no effect). For the homozygous *ApoE4* carrier population treated with lecanemab, rates of ARIA-E ([redacted]) and ARIA-H ([redacted]) were substantially [redacted] than for heterozygous *ApoE4* carriers ([redacted] and [redacted], respectively) or non-carriers ([redacted] and [redacted], respectively). These differential ARIA rates are likely to have consequences for the rates of lecanemab treatment suspension and the associated need for additional safety MRIs and are therefore important considerations in assessing the cost effectiveness of lecanemab in *ApoE4* genotype subgroups.

The EAG noted that the applicability of the Clarity AD trial to the UK setting is uncertain as the trial included [redacted] UK patients. Of particular note, the rates of symptomatic AD treatment (AChEi and memantine) applied in both the lecanemab and placebo arms of the Clarity AD trial appeared to be higher than would be usual in UK clinical practice (established clinical management). Further information, on the different rates of symptomatic AD treatment in study participants with MCI due to AD and those with mild dementia due to AD was provided in response to clarification questions (Table 3.7).[10] For the population with mild dementia due to AD, the proportion of Clarity AD study participants receiving AChEi (approximately [redacted]) was not substantially [redacted] than the 70%, estimated by clinical expert opinion[12] to be typical in the UK. In addition, whilst the proportion of study participants in this group receiving memantine (approximately [redacted]) was substantially [redacted] than the 5%, estimated by clinical expert opinion,[12] the treatment effects of lecanemab increased when patients receiving concomitant treatment with memantine were excluded from the analyses. By contrast, participants in the Clarity AD trial who had MCI appear to have been [redacted]), relative to expectations for the UK; *"I do not know of any reliable current UK data, but my strong impression is that a minority of UK patients with MCI due to AD receive an AChEi and almost none receive memantine."*[12] In addition, the EAG considers that the results of the subgroup analyses for the MCI due to AD population, excluding those receiving concomitant treatment with AChEi or memantine, raise a question about whether lecanemab has a clinically significant effect, in patients with MCI due to AD, when used in the context of UK SoC (i.e., without concomitant symptomatic AD treatment); the adjusted mean difference in change from baseline, for lecanemab versus placebo, at 18 months, for CDR-SB in this subgroup, was [redacted], representing a [redacted]% reduction in decline.[10] This compares to -0.451 (95% CI: -0.669 to -0.233), representing a 27.1% reduction in decline for the ITT FAS+ population.[10]

4 COST EFFECTIVENESS

4.1 EAG comment on company's review of cost effectiveness evidence

This section pertains mainly to the review of cost effectiveness analysis (CEA) studies. However, the search section (4.1.1) also contains summaries and critiques of other searches related to cost effectiveness presented in the company submission. Therefore, the following section includes searches for the CEA review, measurement and evaluation of health effects as well as for cost and healthcare resource identification, measurement and valuation.

4.1.1 Searches performed for cost effectiveness section

The following paragraphs contain summaries and critiques of all searches related to cost effectiveness presented in the CS.[2, 9] The CADTH evidence-based checklist for PRESS, was used to inform this critique. The EAG has presented only the major limitations of each search strategy in the report.[14, 15]

The company provided separate searches to identify published cost effectiveness, HRQoL and direct and indirect cost and resource use associated with all stages of AD, including MCI due to AD and mild, moderate, and severe dementia due to AD. Summaries of the sources searched for each section are provided below:

Table 4.1: Data sources searched for Appendix G: Published cost effectiveness studies (as reported in CS)

Resource	Host/Source	Date Ranges	Date last searched
Electronic databases			
Embase	Embase.com	Inception-2023/08/31	SKR5: 31.8.2023
MEDLINE	Embase.com	Inception-2023/08/31	SKR5: 31.8.2023
MEDLINE-In-Process	PubMed	Inception-2023/08/31	SKR5: 31.8.2023
CENTRAL	Wiley	Inception-2023/08/31	31.8.2023
CDSR	Wiley	Inception-2023/08/31	31.8.2023
CEA Registry	Internet	Inception-2023/08/31	31.8.2023
EconLit	AEAweb.org	Inception-2023/08/31	31.8.2023
NHS EED	Centre for Reviews and Dissemination (CRD) York Database	Inception-2015/03/31	31.8.2023
DARE	CRD York Database	Inception-2015/03/31	31.8.2023
Conferences			
AAIC	2020-23: Internet	2020-2023	Conference searches conducted between 16-20 Oct 2023
EAN	2020: Embase.com 2021-23: Internet	2020-2023	
ANA	2020-23: Annals of Neurology (Wiley)	2020-2023	
AAN	2020-23: Embase.com	2020-2023	
ADI	2020 & 2022 (biennial): Internet	2020-2023	
CTAD	2020-22 (2023 NYP): Internet	2020-2023	

Resource	Host/Source	Date Ranges	Date last searched
ISPOR	2020-23: Internet	2020-2023	
AD/PD	2021-23: Internet (2020 not available)	2020-2023	
Supplementary searches			
RePEc	Internet	Inception-2023/08/31	31.8.2023
OpenGrey	Internet	Inception-2023/08/31	31.8.2023
TRIP	Internet	Inception-2023/08/31	31.8.2023
SCI		Inception-2023/08/31	31.8.2023
Additional Resources			
Additional reviews conducted by Hernandez 2016 and ROADMAP 2017 were used as supplementary sources. [9]			
AAIC = Annual Alzheimer's Association International Conference; AD = Alzheimer's disease; AAN = American Academy of Neurology; ADI = International Conference of Alzheimer's Disease International; ANA = American Neurological Association; CDSR = Cochrane Database of Systematic Reviews; CEA registry = Tufts Medical Center Cost-Effectiveness Analysis Registry; CENTRAL = Cochrane Central Register of Controlled Trials; CS = company submission; CTAD = Clinical Trials on Alzheimer's Disease; DARE = Database of Abstracts of Reviews of Effects; EAN = Annual Congress of the European Academy of Neurology; ISPOR = International Society for Pharmacoeconomics and Outcomes Research; NHS EED = NHS Economic Evaluation Database; PD = Parkinson's disease; RePEc = Research Papers in Economics; SCI = Science Citation Index; TRIP = Turning Research into Practice			

EAG comment: The original search was undertaken in March 2016 and subsequently updated in November 2018, February 2020, June 2021 and August 2023. The CS, Appendix G and the company's response to clarification provided sufficient details (including database host(s), date searched, and date ranges covered) for the EAG to appraise the literature searches.[2, 9, 10]

As observed in Appendix D, strategies were reported in a single table for each resource with the results of the different iterations reported in the final lines. As previously described despite not appearing in the format as suggested by best practice, working on the understanding that all iterations of a search utilised the same strategy as reported in the provided table, strategies appeared well structured and reproducible, and a good range of subject indexing terms (MeSH/Emtree) and free text was used.

A broad range of databases and grey literature sources including conference proceedings and specialist economics resources were searched.

The EAG noted the approach of using a single search conducted to cover both MEDLINE and Embase searches via the Embase.com platform was used, as described in the clinical effectiveness searches, therefore the same limitations will have applied.

Table 4.2: Data sources searched for Appendix H: Health-related quality of life studies (as reported in CS)

Resource	Host/Source	Date Ranges	Date last searched
Electronic databases			
Embase	Embase.com	1990/01/01-2023/08/31	SKR5: 31.8.2023
MEDLINE	Embase.com	1990/01/01-2023/08/31	SKR5: 31.8.2023

Resource	Host/Source	Date Ranges	Date last searched
MEDLINE-In-Process	PubMed	1990/01/01-2023/08/31	SKR5: 31.8.2023
CENTRAL	Wiley	1990/01/01-2023/08/31	SKR5: 31.8.2023
CDSR	Wiley	1990/01/01-2023/08/31	SKR5: 31.8.2023
PsycInfo	Ovid	1990/01/01-2023/08/31	31.8.2023
Conferences			
AAIC	2020-23: Internet	2020-2023	Conference searches conducted between 16-20 Oct 2023
EAN	2020: Embase.com 2021-23: Internet	2020-2023	
ANA	2020-23: Annals of Neurology (Wiley)	2020-2023	
AAN	2020-23: Embase.com	2020-2023	
ADI	2020 & 2022 (biennial): Internet	2020-2023	
CTAD	2020-22 (2023 NYP): Internet	2020-2023	
ISPOR	2020-23: Internet	2020-2023	
AD/PD	2021-23: Internet (2020 not available)	2020-2023	
Supplementary searches			
OpenGrey	Internet	1990/01/01-2023/08/31	31.8.2023
TRIP	Internet	1990/01/01-2023/08/31	31.8.2023

AAIC = Annual Alzheimer's Association International Conference; AD = Alzheimer's disease; AAN = American Academy of Neurology; ADI = International Conference of Alzheimer's Disease International; ANA = American Neurological Association; CDSR = Cochrane Database of Systematic Reviews; CENTRAL = Cochrane Central Register of Controlled Trials; CS = company submission; CTAD = Clinical Trials on Alzheimer's Disease; EAN = Annual Congress of the European Academy of Neurology; ISPOR = International Society for Pharmacoeconomics and Outcomes Research; PD = Parkinson's disease RePEc = Research Papers in Economics; TRIP = Turning Research into Practice

EAG comment: The original searches were undertaken in April 2017 and subsequently updated in December 2018, March 2020, June 2021 and August 2023. The CS, Appendix H and the company's response to clarification provided sufficient details (including database host(s), date searched, and date ranges covered) for the EAG to appraise the literature searches.[2, 9, 10]

As observed in Appendix D: Identification, selection and synthesis of clinical evidence natural history of AD data, strategies were reported in a single table for each resource with the results of the different iterations reported in the final lines. Given the particularly complex nature and high number of searches reported in Table 39 and the PRISMA flowchart Figure 23,[9] combined with the single strategy per resource it was unclear if all searches had been provided. However given that the bottom line for each combined number of hits per resource and the number reported for PRISMA flowchart matched, again working on the understanding that all iterations of a search utilised the same strategy as reported in the

provided table, apart from where a clear addition as in line #27 of the MEDLINE/Embase strategy (Table 40) was reported,[9] strategies appeared well structured and reproducible, and a good range of subject indexing terms (MeSH/Emtree) and free text was used.

A broad range of databases and grey literature sources including conference proceedings and specialist economics resources were searched.

The EAG noted the approach of using a single search conducted to cover both MEDLINE and Embase searches via the Embase.com platform was used as described in the clinical effectiveness searches; therefore, the same limitations will have applied.

Table 4.3: Data sources searched for Appendix I: Cost and healthcare resource identification, measurement and valuation (as reported in CS)

Resource	Host/Source	Date Ranges	Date last searched
Electronic databases			
Embase	Embase.com	2000/01/01-2023/08/31	SKR5: 31.8.2023
MEDLINE	Embase.com	2000/01/01-2023/08/31	SKR5: 31.8.2023
MEDLINE-In-Process	PubMed	2000/01/01-2023/08/31	SKR5: 31.8.2023
CENTRAL	Wiley	2000/01/01-2023/08/31	SKR5: 31.8.2023
CDSR	Wiley	2000/01/01-2023/08/31	SKR5: 31.8.2023
CEA Registry	Internet	2000/01/01-2023/08/31	31.8.2023
EconLit	AEAweb.org	2000/01/01-2023/08/31	31.8.2023
NHS EED	Centre for Reviews and Dissemination (CRD) York Database	2000/01/01-2015.03.31	31.8.2023
DARE	Centre for Reviews and Dissemination (CRD) York Database	2000/01/01-2015/03/31	31.8.2023
Conferences			
AAIC	2020-23: Internet	2020-2023	Conference searches conducted between 16-20 Oct 2023
EAN	2020: Embase.com 2021-23: Internet	2020-2023	
ANA	2020-23: Annals of Neurology (Wiley)	2020-2023	
AAN	2020-23: Embase.com	2020-2023	
ADI	2020 & 2022 (biennial): Internet	2020-2023	
CTAD	2020-22 (2023 NYP): Internet	2020-2023	
ISPOR	2020-23: Internet	2020-2023	

Resource	Host/Source	Date Ranges	Date last searched
AD/PD	2021-23: Internet (2020 not available)	2020-2023	
Supplementary searches			
RePEc	Internet	2000/01/01-2023/08/31	31.8.2023
OpenGrey	Internet	2000/01/01-2023/08/31	31.8.2023
TRIP	Internet	2000/01/01-2023/08/31	31.8.2023
SCI		2000/01/01-2023/08/31	31.8.2023

AAIC = Annual Alzheimer's Association International Conference; AD/PD = Alzheimer's Parkinson's Disease; ANA = American Neurological Association; AAN = American Academy of Neurology; ADI = International Conference of Alzheimer's Disease International; CDSR = Cochrane Database of Systematic Reviews; CENTRAL = Cochrane Central Register of Controlled Trials; CTAD = Clinical Trials on Alzheimer's Disease; EAN = Annual Congress of the European Academy of Neurology; ISPOR = International Society for Pharmacoeconomics and Outcomes Research; RePEc = Research Papers in Economics; SCI = Science Citation Index; TRIP = Turning Research into Practice

EAG comment: The company provided a timeline of the five searches undertaken and the search strategies used. The original search was undertaken in May 2017 and subsequently updated in December 2018, March 2020, June 2021 and August 2023. The CS, Appendix I and the company's response to clarification provided sufficient details (including database host(s), date searched, and date ranges covered) for the EAG to appraise the literature searches.[2, 9, 10]

The company reported that these searches were an extension and update of a previously conducted review by (Schaller 2015).[9]

As observed in Appendix D: Identification, selection and synthesis of clinical evidence natural history of AD data, strategies were reported in a single table for each resource with the results of the different iterations reported in the final lines. As previously described, despite not appearing in the format as suggested by best practice, working on the understanding that all iterations of a search utilised the same strategy as reported in the provided table, strategies appeared well structured and reproducible, and a good range of subject indexing terms (MeSH/Emtree) and free text was used.

A broad range of databases and grey literature sources including conference proceedings and specialist economics resources were searched. As previously reported the conference searches utilised the same keywords as all other SLRs conducted as part of the CS.

The EAG noted the approach of using a single search conducted to cover both MEDLINE and Embase searches via the Embase.com platform was used as described in the clinical effectiveness searches; therefore, the same limitations will have applied.

4.1.2 Inclusion/exclusion criteria

In- and exclusion criteria for the review on cost effectiveness studies, HRQoL studies and costs and resource use studies are presented in Table 4.4.

Table 4.4: Eligibility criteria for the systematic literature reviews

	Inclusion criteria	Exclusion criteria
Patient population	Adult (≥18 years) patients with MCI (irrespective of causality) and/or AD (irrespective of severity).	Patients with a specific type of dementia other than AD, e.g., Parkinson's, vascular dementia, or frontotemporal dementia. Studies evaluating children.
Intervention	No restriction	Not applicable
Comparator	No restriction	Not applicable
Outcomes(s) 1 (Published economic evaluations)	Summary of the model where available (type, time-horizon, perspective, discount rate, cycle length, health states), data sources, costs, QALYs, and ICER.	Studies not reporting relevant outcomes of interest.
Outcomes(s) 2 (HRQoL studies)	Information on recruitment, response rates, description of health states, adverse reactions, appropriateness of health states, care setting, methods of elicitation/valuation, mapping, and uncertainty around values	Studies not reporting relevant outcomes of interest.
Outcomes(s) 3 (Cost/resource use studies)	Resource use data, cost valuation details, technology costs, costs for use in economic analysis, and caregiver time (hours) spent on providing care.	Studies not reporting relevant outcomes of interest.
Study design 1 (Cost effectiveness analysis studies)	Economic evaluations	Non-economic evaluations
Study design 2 (HRQoL studies)	No restriction: all the interventional and observational studies will be considered for inclusion. • Experiment and quasi-experimental studies • Prospective and retrospective studies • Registry/database-driven studies	Not applicable
Study design 3 (Cost/resource use studies)	No restriction: all the interventional, observational, and register-based studies will be considered for inclusion. • Prospective studies reporting costs or resource utilisation (e.g., observational	Not applicable.

	Inclusion criteria	Exclusion criteria
	studies, clinical trials, cross-sectional studies) • Retrospective studies reporting costs or resource utilisation (e.g., cost-of-illness, database studies)	
Based on CS appendices G, H and I[9] AD = Alzheimer's disease; CS = company submission; HRQoL – health-related quality of life; ICER = incremental cost-effectiveness ratio; MCI = mild cognitive impairment; QALY = quality-adjusted life years		

EAG comment: The company conducted additional hand searches to identify studies reporting rates of institutionalisation, mortality, mapping algorithms, and health state costs. However, details regarding these hand searches were initially not provided. In response to clarification, the company explained that the utilised search engine was Google Scholar, and that the hand search utilised simple search terms. It is unclear to the EAG why the resulting studies from these simple hand searches were not identified in the full SLR.

4.2 Summary and critique of company's submitted economic evaluation by the EAG

4.2.1 NICE reference case checklist

Table 4.5: 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	Consistent
Perspective on costs	NHS and PSS	Partly, direct non-medical costs include costs outside of NHS and PSS perspective on costs.
Type of economic evaluation	Cost utility analysis with fully incremental analysis	Consistent
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	Consistent
Synthesis of evidence on health effects	Based on systematic review	Partly, the company also included evidence that was non-systematically identified (e.g., hand searching).
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.	Consistent, notably, caregiver QALYs were included.
Source of data for measurement of health-related quality of life	Reported directly by patients and/or carers	Consistent, notably proxy values were utilised for some patient health-related quality of life data.

Element of health technology assessment	Reference case	EAG comment on company's submission
Source of preference data for valuation of changes in health-related quality of life	Representative sample of the UK population	Consistent
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Consistent
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	Partly, some unit prices are not in line with the NHS England Alzheimer's MCI model
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	Consistent

EAG = Evidence Assessment Group; EQ-5D = European Quality of Life-5 Dimensions; NHS = National Health Service; PSS = Personal Social Services; QALY= quality adjusted life years

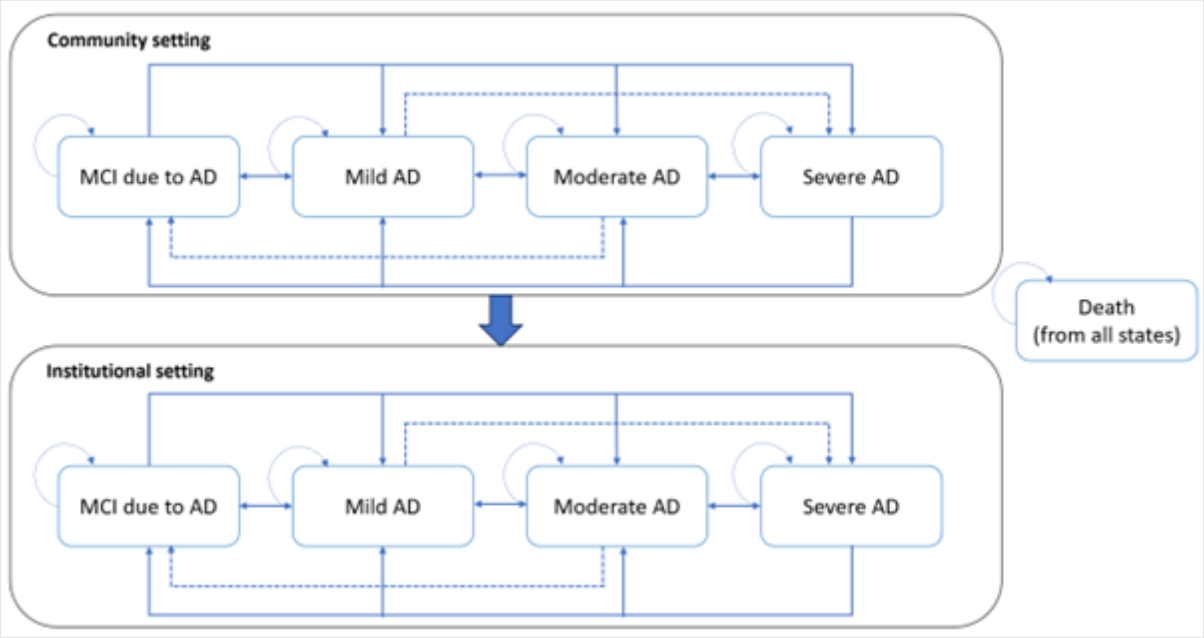
4.2.2 Model structure

The company developed a state transition model (in MS Excel) including four health states based on AD severity that were replicated in the community and institutional care settings: MCI due to AD, mild AD, moderate AD, severe AD, and death (nine health states in total) (see CS Figure 31 and Figure 4.1 below). Model health states were defined by AD severity according to CDR-SB (and global CDR in a scenario, based on feedback from clinical experts at the UK Health Technology Assessment [HTA] advisory board), both of which are established clinical assessment of disease severity in AD. Moreover, using CDR-SB aligns with the primary endpoint of the pivotal trial (Clarity AD). Company submission Table 3 provides an overview of how CDR-SB and Global CDR ratings were mapped to AD severity: for CDR-SB this was 0.5-4.0 for MCI due to AD, 4.5-9.0 for mild AD, 9.5-15.5 for moderate AD and 16.0-18.0 for severe AD.

The company stated that a state transition model was more suitable than a discrete event simulation (DES), which was used in seven of the 20 studies identified by the SLR, due to the increased computational burden and associated requirement for software other than MS Excel, and the resulting loss of transparency compared with cohort models.

All patients were assumed to start in the 'MCI due to AD' or 'Mild AD' health states in the community setting, as per the pivotal trial (Clarity AD). Patients can transition between all disease severity levels within community and institutional care settings in each cycle, however they cannot return to the community setting once institutionalised. The company stated that backwards transitions (i.e., to milder health states) are permitted.

Figure 4.1: Model structure



Based on Based on Figure 31 in the CS[2]
AD = Alzheimer's disease; CS = company submission; MCI = mild cognitive impairment

EAG comment: The main concerns of the EAG relate to: a) the use of CDR-SB to define health states and; b) the inclusion of backward transitions.

a) The EAG noted that according to a recent publication from the International Pharmaco-Economic Collaboration on Alzheimer's Disease (IPECAD) modelling challenge comparing cost effectiveness models for Alzheimer's disease and related dementia (Handels et al,[29]; Table 3), the MMSE and CDR-SB are both commonly used to define AD health states (i.e., AD severity). The company used CDR-SB (not MMSE) for defining health states. In clarification response B5, the company clarified that "*CDR-SB was chosen to define model health states in favour of MMSE, given that CDR-SB has been demonstrated to adequately detect slowing of progression with manageable sample sizes in the early AD patient population, whilst MMSE has not*" and that "*CDR-SB assesses both cognition and function, while MMSE is designed to assess cognition only*". The clinical expert consulted by the EAG confirmed that CDR-SB is well established in research practice and clinical trials, incorporates both cognition and function into a single measure and is sensitive to decline from a very early stage. However, it was also noted by the clinical expert, that in UK practice, staging of AD is nearly always subjective, relying on clinical experience and diagnostic criteria (e.g., Diagnostic and Statistical Manual of Mental Disorders (DSM),[30] NIA-AA[31]) rather than specific staging tools (such as CDR-SB and MMSE). The distinction between MCI and mild AD is in clinical practice based solely on a clinical judgement about whether there is any significant functional impairment. There is a lot of variability between individual clinicians. Overall, the EAG believes the model structure adopted in the CS to be reasonable.
b) The company clarified (response to question B6) that backward transitions were permitted and that this was consistent with half of the IPECAD models. Although clinical expert opinion, provided by the company, indicated that "*such improvements are feasible but may only be temporary*", the company justified that backward transitions were "*deemed appropriate in this context given the model uses a relatively short cycle length of one month, therefore such 'improvements' are likely to be temporary*". In response to clarification question B6c, where it

was asked how backwards transitions were included in the economic model, the company referred to CS Table 39 which provides the health state occupancy as defined by CDR-SB at month 18. Considering the above, the EAG believes it is not unreasonable to include backward transitions.

4.2.3 Population

Consistent with the NICE scope, the population considered in the CS (CS Table 1) was people with MCI due to AD or mild dementia due to AD (early AD) and confirmed Aβ pathology in alignment with the anticipated positioning of lecanemab (CS Section B.1.1). The baseline population characteristics used in the analysis (CS Table 37 and Table 4.6 below) are reflective of the Clarity AD ITT population. To reflect the final scope, subgroup analyses were presented by the company based on the MCI due to AD and mild AD clinical subgroups (CS Section B.3.11.3). No subgroup analysis was provided based on apolipoprotein E 4 (ApoE4) gene carrier status.

Table 4.6: Key baseline patient characteristics (based on Clarity AD)

Patient characteristics	CS base-case (CS Table 37)	ITT FAS+ (CSR Table 14.1.4.1.1)	ITT FDA FAS (CSR Table 14.1.4.1.2)	SAS (CS Table 10 and CSR Table 14.1.4.1.3)
Age (years, mean [SD])	71.2 (7.8)	[redacted]	[redacted]	[redacted]
Female (proportion)	52.3%	[redacted]	[redacted]	[redacted]
Weight, kg (mean [SD])	69.8 (12.5)	[redacted]	[redacted]	[redacted]
Baseline MCI due to AD (proportion)	78.8%	[redacted]	[redacted]	[redacted]
Baseline mild AD dementia (proportion)	21.2%	[redacted]	[redacted]	[redacted]

AD = Alzheimer's disease; CS = company submission; CSR = clinical study report; FDA = Food and Drug Administration; FAS = full analysis set; ITT = intention-to-treat; MCI = mild cognitive impairment; SAS = safety analysis set; SD = standard deviation

EAG comment: The main concerns of the EAG relate to: a) missing subgroup based on *ApoE4* gene carrier status; b) the representativeness of the Clarity AD population to UK clinical practice and; c) analysis set used to inform population characteristics in the CS base-case.

a) The missing subgroup analysis (specified in the scope), based on *ApoE4* gene carrier status, were helpfully provided by the company in response to clarification question A9 as well as Table 54 in the clarification response document. This indicated that compared to the company base-case, the incremental cost-effectiveness ratio (ICER) would [redacted] for the *ApoE4* non-carrier subgroup while it [redacted] for the *ApoE4* homozygotes subgroup ([redacted]) and *ApoE4* heterozygotes subgroup ([redacted]).
b) In Clarity AD, [redacted] had MCI and [redacted] had mild dementia (see Table 4.6 above). In the UK, patients are currently more likely to present at the mild dementia than MCI stage, and so the proportions offered lecanemab might be reversed (i.e., [redacted] MCI, [redacted] mild dementia) according to clinical opinion obtained by the EAG. This is supported by the company's response to clarification question B7. Additionally, approximately 70% of participants in Clarity AD were

ApoE4 carriers. The Alzheimer's Society suggest the figure in the UK is nearly "two out of three", based on clinical expert opinion obtained by the EAG this would approximately be 65% which is confirmed by a Northern Europe study (not including the UK) indicating 63%.[32] In conclusion, the proportion of *ApoE4* carriers in Clarity AD might be slightly higher than in UK clinical practice, potentially resulting in a slight overestimation of the base-case ICER. Conversely, the proportion of patients starting with MCI might be substantially overestimated (see also key issue 7), potentially resulting in a substantial underestimation of the ICER (according to CS Table 70 the list price ICER for the mild AD subgroup [redacted] versus [redacted] respectively). To reflect UK clinical practice more closely, the baseline proportion of patients with MCI and mild dementia was changed to [redacted] and [redacted] respectively in the EAG base-case.

c) The population characteristics used in the CS base-case are provided in CS Table 37. This Table refers to CSR Table 14.1.4.1.1 as a source for the values used for age, proportion of females and weight and CSR Table 14.2.3.8.1 for baseline proportions for MCI due to AD and mild AD. The CSR Table 14.1.4.1.1 reports on the ITT FAS+, however the weight reported in CS Table 37 is inconsistent with CSR Table 14.1.4.1.1 (69.8 versus [redacted]; see Table 4.6 above). Moreover, the baseline proportions reported for MCI due to AD and mild AD are in CSR Table 14.2.3.8.1 (and used in the CS base-case) are inconsistent with those reported for the ITT FAS+, ITT Food and Drug Administration (FDA) FAS and SAS in CSR Tables 14.1.4.1.1-14.1.4.1.3. The EAG presumes that this difference can be explained by the definition of MCI due to AD and mild AD, either through CDR-SB (CS base-case; CS Table 37) or case report form (CS Table 10), both based on the ITT FAS+.

4.2.4 Interventions and comparators

The comparator, established clinical management, was defined in the final scope as non-pharmacological management for MCI due to AD, and an AChEis (donepezil, rivastigmine, and galantamine according to NG97) plus non-pharmacological management for mild AD. As described in Section 2.2, the company amended the comparator for mild AD to including no AChEi. The proportion of patients receiving symptomatic treatments (i.e., AChEis or memantine) differs by health state and is informed by Clarity AD (CS Table 52).

The intervention in the final scope was defined as lecanemab plus established clinical management. Consistently, in Clarity AD, patients were allowed to continue receiving symptomatic AD medication during the study alongside lecanemab. Lecanemab is assumed to be administered biweekly at a dose of 10 mg/kg via IV infusion over approximately one hour per Clarity AD and the draft SmPC (CS Appendix C). The company assumed that treatment with lecanemab was discontinued when patients progressed to moderate/severe AD or once patients were institutionalised (regardless of AD severity).

EAG comment: The main concerns of the EAG relate to: a) potential mismatch between Clarity AD and UK clinical practice in terms of established clinical management and; b) treatment stopping rule for lecanemab.

a) According to CS Table 52, AChEis and memantine are provided in all health states (though the proportions of patients receiving these symptomatic treatments are health state specific). This is inconsistent with NG97 stating that AChEis should be provided to mild AD (not MCI due to AD) and that memantine is an option for severe AD, or moderate AD ineligible for AChEis. This was confirmed by clinical expert opinion, obtained by the EAG, stating that the minority of UK patients with MCI due to AD receive AChEis and almost none receive memantine. Moreover, it was stated that AChEis and memantine will be administered to approximately

70% and 5% of people with mild AD respectively. Although the cost consequences of these differences in symptomatic treatments might be very minor (CS Table 54), it illustrates the potential mismatch between Clarity AD and UK clinical practice in terms of established clinical management which might have implications for the estimated (relative) effectiveness. When comparing CS Tables 16, 18, 19 and 20 with the Tables provided by the company in response to clarification questions B5 and B6, [redacted], see also key issues 2, 3 and 7.

b) In addition to all-cause treatment discontinuation, a stopping rule for lecanemab discontinuation was assumed upon progression to moderate/severe AD or institutionalisation. This was based on clinical expert opinion due to the absence of data from Clarity AD. However, based on CS Table 11, 22% patients did discontinue treatment, most patients discontinued due to adverse events (8%) or due to withdrawal of consent (8%), and none discontinued treatment due to inadequate therapeutic effect. Hence this does not support the stopping rule assumed by the company. Nevertheless, based on clinical expert opinion obtained by the EAG, it seemed reasonable to discontinue lecanemab upon progression to moderate/severe AD, given that there is no evidence that any anti-amyloid drugs are effective in moderate/severe dementia. It might also be a requirement of the marketing authorisation if only granted for MCI due to AD or mild AD. However, the feasibility of implementing such a stopping rule in UK clinical practice was questioned by the clinical expert consulted by the EAG, given that CDR-SB is not currently used in clinical practice and there may also be considerable resistance from patients and families. Additionally, the clinical expert stated that few patients are likely to be institutionalised before progressing to moderate/severe AD, but those patients with mild dementia who are institutionalised should not automatically have their treatment discontinued, but a decision made depending on individual circumstances. Therefore, the EAG explored a scenario disabling lecanemab treatment discontinuation after institutionalisation.

4.2.5 Perspective, time horizon and discounting

The analysis is performed from the NHS and Personal Social Services (PSS) perspective. Discount rates of 3.5% are applied to both costs and benefits. The model cycle length is one month with a lifetime time horizon and a half-cycle correction is applied.

EAG comment: The model has a 30-year time horizon which is effectively lifetime. The estimated costs are only partly consistent with the NHS and PSS perspective, as direct non-medical costs include costs outside of NHS and PSS perspective on costs.

4.2.6 Treatment effectiveness and extrapolation

The main source of evidence on treatment effectiveness for lecanemab was the Clarity AD study, an 18-month Phase III study that is used to inform the marketing authorisation of lecanemab for patients with early AD. Clarity AD informed the transition probabilities with which patients transit from MCI due to AD and mild AD to the other health states for both treatment arms in the first 18 months of the model, and transition probabilities were estimated separately for both arms. Beyond the 18 months trial duration, a SLR on natural history published data was conducted to inform the natural disease progression for SoC. Treatment effectiveness beyond 18 months for the lecanemab arm was modelled using the hazard ratios derived from Clarity AD, which reflected the 18-month trial period and was assumed constant beyond that. The two hazard ratios for time-to-worsening (for transitions from MCI

due to AD and mild AD) were derived using a Cox proportional hazards model based on the time-to-worsening, which in turn was estimated using CDR-SB scores.

4.2.6.1 Baseline characteristics

The company used baseline characteristics in the economic model that they stated were reflective of the Clarity AD ITT population (Table 4.7).

Table 4.7: Baseline patient characteristics in the model

Patient characteristics	Value (SE)	Source
Age (years, mean)	71.2% (7.84)	Clarity AD, Table 14.1.4.1.1
Female (proportion)	52.3% (0.01)	
Weight, kg (mean [SD])	69.8 (12.54)	
Baseline health state MCI due to AD	78.8% (0.01)	Clarity AD, Table 14.2.3.8.1
Baseline health state mild dementia due to AD	21.2% (0.01)	
Based on CS Table 37[2] AD = Alzheimer's disease; CS = company submission; kg = kilogram; MCI = mild cognitive impairment; SD = standard deviation; SE = standard error		

4.2.6.2 Transition probabilities based on Clarity AD

During the first 18 months, transition probabilities for both lecanemab and SoC were derived from the empirical data for both arms in Clarity AD without requiring treatment effect parameterisation. The 18-month transition probabilities were converted to one-month and were assumed to be constant during the first 18 months. Patients who discontinued the treatment during the first 18 months for all-cause discontinuation, did not have data imputed and were excluded from the analysis. The transition probabilities for the first 18 months are summarised in Table 4.8. Transitions to less severe AD stages, that is backward transitions, were observed in Clarity AD, and natural history data and supported by clinical expert opinion from the advisory board.[33]

Table 4.8: Monthly transition rates for both arms in the first 18-months based on Clarity AD

Monthly transitions probabilities	SoC	Lecanemab
From MCI		
to MCI	[redacted]	[redacted]
to Mild AD	[redacted]	[redacted]
to Moderate AD	[redacted]	[redacted]
to Severe AD	[redacted]	[redacted]
From Mild AD		
to MCI	[redacted]	[redacted]
to Mild AD	[redacted]	[redacted]
to Moderate AD	[redacted]	[redacted]
to Severe AD	[redacted]	[redacted]
Based on CS model, clinical data tab AD = Alzheimer's disease; MCI = mild cognitive impairment; SoC = standard of care		

4.2.6.3 Estimation of natural history beyond 18 months

To inform transition probabilities beyond the 18 months in the SoC arm, an SLR was conducted to identify published natural history data. In total, 40 studies reporting AD transition probabilities were

identified and reviewed to determine their relevance to the economic analysis, with the criterion of having a population with confirmed Aβ pathology to ensure the baseline risk of disease progression in the model is reflective of the target population. Among the 40 studies, none were specific to the UK, and only three reported results for a population with confirmed Aβ. Of these three studies, only one, Potashman et al, was deemed an appropriate source for transition probabilities across the disease stages.[33] Potashman et al. was chosen based on longitudinal patient-level data for a subset of patients in the National Alzheimer's Coordinating Center (NACC) database, which was preferred by clinicians in the advisory board.

The progression rates that were used from Potashman et al. to inform the transition probabilities beyond the 18 months in the model were estimated through asymptomatic, MCI due to AD, mild AD, moderate AD, severe AD, and death stages.[33] These transitions were reported as annual progression probabilities and converted to monthly rates by taking the 12th root of the transition matrix, computed via the eigen decomposition method using the EXPM package in R. Monthly transition probabilities beyond the 18 months, as summarised in Table 4.9 were updated in the company response to the clarification letter, using transition probabilities as reported directly from Potashman et al. instead of the probabilities that were reported by Herring et al. based on Potashman et al. in the original submission.[34] Transitions to the asymptomatic health state were added to the probability of moving to, or remaining in, the MCI-AD state, reflecting the methodology used in Herring et al. The remaining probabilities were re-weighted across transitions to alive health states to create the matrix for use in the model. Table 4.9: Monthly transition rates beyond the 18 months based on Potashman et al.

Table 4.9: Monthly transition probabilities

Monthly transitions probabilities	SoC	Lecanemab
MCI due to AD		
Mild AD	1.5%	[redacted]
Moderate AD	0.5%	[redacted]
Severe AD	0.0%	[redacted]
From Mild AD		
to MCI due to AD	0.3%	[redacted]
to Moderate AD	3.5%	[redacted]
to Severe AD	0.4%	[redacted]
From Moderate AD		
to MCI due to AD	0.0%	[redacted]
to Mild AD	0.2%	[redacted]
to Severe AD	4.4%	[redacted]
From Severe AD		
to MCI due to AD	0.0%	[redacted]
to Mild AD	0.0%	[redacted]
to Moderate AD	0.2%	[redacted]

Based on Updated CS model in 30th of January 2024, natural history transition tab
AD = Alzheimer's; CS = company submission; MCI = mild cognitive impairment; SoC = standard of care

4.2.6.4 Relative effectiveness

Treatment effect was not parameterised in the first 18 months as the transition probabilities were calculated from the distribution of patients across each health state based on CDR-SB as observed in

Clarity AD. Beyond 18 months, the lecanemab treatment effect on AD progression was modelled via a hazard ratio based on all available patients at risk of transition while censoring patients that have not had an event. The hazard ratio was estimated using a Cox proportional hazards model separately for patients starting in MCI due to AD and mild AD.

Following Clarity AD methodology, the analysis for time to worsening, with worsening defined as progression from MCI due to AD to mild AD, or from mild AD to moderate AD of global CDR score at 18 months was applied to CDR-SB, yielding a hazard ratio (0.69) for lecanemab versus placebo. This analysis, aligning with the base-case and the model structure, was separately conducted for MCI due to AD and mild AD patients, defining time to worsening as days from randomisation to a confirmed CDR-SB worsening score. Time was censored at the last CDR assessment in the absence of an observed event.

The company assumed in the base-case that lecanemab treatment effect was constant for both patients who remained on treatment, and for those who discontinued due to all-cause discontinuation. According to the CS, the hazard ratios that were estimated under the ITT principle reflected the impact of all-cause discontinuations in lecanemab treatment effect, and therefore it was assumed to be constant. Hazard ratios that were based on global CDR were used as a scenario analysis.

4.2.6.5 Time To Discontinuation

All-cause treatment discontinuation was modelled as a constant rate, and was based on Clarity AD. The lecanemab arm had a [redacted] discontinuation rate, resulting in a monthly all-cause discontinuation rate of [redacted] based on [redacted] discontinuation events and total cumulative exposure time of [redacted] patient-years (summation of all patients' exposure to treatment durations).

Clarity AD did not include a treatment stopping rule for lecanemab. Currently, there is no consensus among UK clinical experts on which stopping rule will be applied to lecanemab in clinical practice. According to the CS, the advisory board emphasised that the overriding principle for stopping the treatment should be to prolong patients' time at the earlier stages of disease in which they have a better quality of life (QoL). The Institute for Clinical Economic Review (ICER) assessment of lecanemab assumed that people stop treatment upon progression to moderate AD. The advisory board also agreed that patients discontinue lecanemab once they have been institutionalised, regardless of the disease severity. Therefore, the cost effectiveness model included stopping rules for progression to moderate AD and entering institutional care, to reflect UK clinical expert opinion. The company modelled the stopping rule in the cost effectiveness model to affect the costs of lecanemab and transition probabilities of patients in the AD health states.

4.2.6.6 Risk of institutionalisation

Rates of institutionalisation were not available from Clarity AD, and data identified through the natural history SLR were sparse. A hand search was conducted by the company, and it identified two UK studies (Knapp et al. and Belger et al.) that did not have an Aβ-confirmed population but reported the risk of institutionalisation by AD severity according to MMSE. Therefore, these studies were used to inform the cost effectiveness model.[35, 36]

Knapp et al. was selected for the base-case analysis as it reported risk of institutionalisation based on a larger sample than Belger et al.[35, 36] Knapp et al. reported six-month probabilities of institutionalisation in mild AD, moderate AD, and severe AD, that were converted to monthly probabilities to align with the model cycle length. Patients with MCI due to AD were assumed to have no risk of institutionalisation, which aligned with the other AD studies and with the opinion of the UK HTA

advisory board. Belger et al. was used in a scenario analysis, for which the 3-year institutionalisation probabilities were converted to monthly probabilities to align with the model cycle length. The monthly probabilities of transitioning to institutionalised care increased with increasing severity of disease as summarised in Table 4.10.

Table 4.10: Monthly probabilities of institutionalisation for both treatment arms

Monthly institutionalisation probabilities	Base-case	Scenario analysis
Health state	Knapp et al. 2016[35]	Belger et al. 2019[36]
MCI due to AD	0%	0%
Mild AD	0.51%	0.43%
Moderate AD	1.38%	0.82%
Severe AD	1.74%	0.90%
AD = Alzheimer's; MCI = mild cognitive impairment		

4.2.6.7 Mortality

Population mortality was informed by the Office for National Statistics 2022/2023 population life tables for England and Wales and adjusted by age and sex for excess mortality associated with AD. Mortality was applied as the sex-weighted annual mortality adjusted to the monthly cycle length. The model required mortality estimates for MCI due to AD, mild, moderate, and severe AD health states defined using CDR-SB. An SLR was carried out for identifying studies with confirmed Aβ pathology population, that reports mortality rates for the different health states and estimates that were relative to the general population. According to the CS, none of the natural history studies met these criteria. Therefore, a hand search was carried out, which identified one study that reported relative mortality rates across all stages of AD based on NACC data. The Crowell et al. study also included patients with confirmed Aβ pathology and used Cox proportional-hazards models adjusting for age, sex, and years of education.[37] This study estimated a decreased risk of death in MCI due to AD when compared with the cognitively normal group. Table 4.11 summarises the mortality hazard ratio by disease state.

Table 4.11: Mortality hazard ratio by disease state

Health state	Hazard ratio
MCI due to AD	0.63
Mild AD	2.43
Moderate AD	3.77
Severe AD	8.53
Based on CS table 43[2] AD = Alzheimer's; CS = company submission; MCI = mild cognitive impairment	

EAG comment: The main concerns of the EAG relate to: a) the use of ITT population for baseline characteristics, b) estimation of transition probabilities from Clarity AD; c) potential time variation in transition probabilities; d) potential long-term treatment effect; e) the choice of mortality rates; f) the treatment stopping rules, and g) the source of institutionalisation rates used in the model.

a) The company stated that the baseline characteristics used in the model were in line with clinical expert opinion. However, it became clear that what was presented to clinical experts was not what was used in the model but was instead based on CS appendix N Table 62. It was unclear in the first place what explained the differences, but finally the company provided a table overview showing how baseline characteristics were derived. The proportions used in the

model were based on the baseline state membership based on CDR-SB; while the proportions shown in the appendix were based on the case report form. The EAG noted this discrepancy and asked for further explanation of what experts had actually considered in line with the UK population. In their response to clarification question B7, the company stated that UK clinical expert feedback was sought on proportions MCI due to AD [redacted], so not on what was used in the model. One clinician stated that the proportions observed in Clarity AD are unreflective of the proportions of people who have MCI due to AD versus mild AD in the UK population. Another clinician consulted by the company argued that the proportions are expected to change over time and are likely to reflect clinical practice. A third clinician noted that the initial prevalence of MCI due to AD was still unclear. The EAG's clinical expert stated that the proportions from the modified intention-to-treat (mITT) population are more likely to be reversed (i.e., [redacted]), as patients in the UK are more likely to show up at the mild AD stage. To reflect UK clinical practice more closely, the baseline proportion of patients with MCI due to AD and mild AD was changed to [redacted] respectively in the EAG base-case.

b) There are concerns about the company's estimation of transition probabilities.
   - Transition probabilities for the first 18 months in the model were calculated excluding patients who did not complete the core study in Clarity AD due to early discontinuation from AEs, withdrawal of consent, or loss to follow-up. The EAG was concerned that this might introduce bias and requested a scenario analysis that included the discontinued patients in the cost effectiveness model, by assuming they had progressed to moderate AD. This scenario was provided by the company and led to an ICER increase of £[redacted] ([redacted]%) in the corrected company base-case (without PAS) compared with the initial company base-case. Given that the impact is minor, and that this is a rather pessimistic scenario (for lecanemab), the EAG kept the company's assumption excluding patients who did not complete the core study in Clarity AD in its base-case, and explored including these in a scenario.
   - The company included backward transitions in the cost-effectiveness model to reflect transitions from a more severe health state to a milder health state. The company explained that backward transitions were consistent with half of the IPECAD models and were deemed appropriate given that the model has a short cycle length of one month, and that such backward transitions were likely to be temporary. The clinical expert opinion also indicated that these transitions are plausible but may only be temporary. In response to clarification question B8.b, the company explained how these backward transition probabilities were derived from Clarity AD and implemented in the cost-effectiveness model. Beyond 18 months, no treatment effect was included on backward transitions, which appears appropriate. The EAG explored a scenario analysis excluding backward transitions, which increases the ICER substantially, from the company base-case ICER (with PAS) [redacted] to [redacted].
   - Assuming constant transition probabilities may be questionable. The company helpfully performed extensive analyses to explore the appropriateness of assuming constant transition probabilities in the first 18 months of the model time horizon and beyond. While data for time-varying analyses were not available from Potashman et al, the company performed multistate survival analysis on Clarity AD data to estimate transition probabilities over time that were used to inform the first 18 months in the model.[33] Transitions to severe AD and death were not included due to small numbers of observations and were instead informed by Potashman et al. and Crowell et al.

respectively (in alignment with the company's updated base-case).[37] The company stated that the analysis was conducted using a clock-forward (Markov) approach to enable time-dependent transition probabilities, which means that transition probabilities were still dependent on time spent in previous states as opposed to being dependent only on the time spent in the current state. The company stated that a clock-reset approach would require altering the model structure to include tunnel states and would not have been feasible within the timeframe for clarification question responses. The company stated that, given that a clock-forward approach was used, observations were considered using time from the start of the study (i.e., at baseline) for each patient, as opposed to time since entry into each health state. As a consequence, patient numbers at risk increased for all transitions other than that from MCI due to AD to mild AD. The EAG considers this approach appropriate.

For the survival analysis, joint modelling was used with treatment being a covariate, which the company considered was supported by the smoothed hazard plots and the proportional hazard assessment for the time-to-worsening analysis, and the EAG agrees that this appears appropriate. Different statistical models were fitted for each transition. The company considered statistical fit (Akake information criterion/Bayesian information criterion (AIC/BIC statistics)), but in the end mostly based their choice for the Weibull distribution on the pattern of hazard (i.e., increasing hazards over time, whereas the best-fitting generalized gamma, lognormal and loglogistic exhibited decreasing hazards over time). The EAG considers that this was likely appropriate. Transition probabilities are shown in Table 4.12.

The company still maintained the use of the NACC data (and constant transition probabilities) after the 18 months' time point in the model. The company justified this by stating that these data were likely more appropriate than the trial data which are only available until 18 months, and any overfitting may lead to transition probabilities beyond 18 months that are not aligned with the underlying risk. Using the multistate model instead of the constant transition probabilities up to 18 months reduces the patient access scheme (PAS) ICER to [redacted]. The company's analyses showed general similarity in life-years estimated for each health state between the multistate survival models extrapolated over the model time horizon and the company's updated base-case which used constant transition probabilities (Table 61 in response to clarification letter). Given the trend towards an increase in the rate at which patients transition from MCI due to AD to mild AD, mild AD to moderate AD, and mild AD to MCI due to AD over time, and the fact that the exponential distribution provided the worst fit to the data for most transitions except the one from moderate AD to mild AD, the EAG considers that exploring time-dependent transitions in future AD assessments and in future analyses for this appraisal may be important. The EAG explores the use of a scenario using the company's multistate survival model transition probabilities. The EAG also notes that it remains unclear how competing events were handled in this analysis and recommends that this be clarified by the company.

Table 4.12: Time-dependent transition probabilities as estimated by the multistate survival analysis

Cycle (months)	Lecanemab				SoC			
	MCI to Mild AD	Mild AD to MCI	Mild AD to moderate AD	Moderate AD to mild AD	MCI to Mild AD	Mild AD to MCI	Mild AD to moderate AD	Moderate AD to mild AD
1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
7	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
8	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
9	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
10	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
11	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
13	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
14	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
15	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
16	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
17	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
18	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

AD = Alzheimer's; MCI = mild cognitive impairment; SoC = standard of care

- As highlighted in clarification question B10, the company did not follow the tutorial by Gidwani et al. to derive transition probabilities for multiple health states and their conversion to a different period length matching the cycle length.[38] This can introduce significant errors in the calculation of numbers of patients in each health state due to competing risks, i.e., when more than two transitions are possible within a cycle. The company tried to implement the second proposed solution by Gidwani et al. (i.e., calculate the eigen decomposition of the transition matrix), but noted that this resulted in some negative transition probabilities, which is a known problem. The EAG agrees that this method is not appropriate. The company considered the first solution proposed by Gidwani et al. (i.e., revising the model structure so that each node only has two model transitions) as impossible, *"as this would require severely limiting structural assumptions, for example restricting patients movement so that patients can only remain in their current health state, or progress to the next most severe health state in any given cycle, which would not be consistent with the natural history data"* and did not implement this method. The EAG would like to see this explored as there may be a way of considering multiple transitions with the appropriate changes to the model structure, e.g., considering whether a patient progressed or regressed or not, etc. It is however true that this model might become "bushy". The company has since also provided an alternative method for estimating transition probabilities, i.e., the multistate survival analysis described above. The EAG compared the results of the multistate survival analysis, when using the exponential distribution (i.e., constant transition probabilities) with the company's original transition probabilities. Results show large discrepancies between the original and new transition probabilities (Table 4.13). This seems to suggest that the original transition probabilities may not be appropriate.

Table 4.13: Comparison of transition probabilities as derived in the original model versus the multi state survival analysis

Health state transitions	Original transition probabilities	Multistate survival analysis (using exponential) transition probabilities
Lecanemab		
MCI due to AD to mild AD	[redacted]	[redacted]
Mild AD to MCI due to AD	[redacted]	[redacted]
Mild AD to moderate AD	[redacted]	[redacted]
Moderate AD to mild AD	[redacted]	[redacted]
SoC		
MCI due to AD to mild AD	1.5%	[redacted]
Mild AD to MCI due to AD	0.3%	[redacted]
Mild AD to moderate AD	3.5%	[redacted]
Moderate AD to mild AD	0.2%	[redacted]
Based on Company's original and updated models AD = Alzheimer's; MCI = mild cognitive impairment; SoC = standard of care		

Given that there are problems with the external and cross validation of the model results (see Section 5.3, including that transitions from mild to moderate AD are substantially

lower in the first 18 months compared to the post-18 months period), the EAG recommends exploring this further, and is particularly interested in how the company handled potential competing risks in the multistate survival analysis and whether the company consider this analysis to be more appropriate for the base-case.

c) The company assumed no treatment effect waning while patients were modelled to be on treatment, and assumed [redacted] waning upon treatment discontinuation in the model. This assumption was made as there is no evidence from Clarity AD regarding long-term treatment effects beyond the 18th month. In response to clarification question B11.d, the company stated that 81.2% of lecanemab patients completed the Clarity AD core study. They assumed that patients will remain on treatment beyond the 18 months in clinical practice which resulted in a modelled mean time-on-treatment of [redacted] years. Since [redacted] treatment effect waning was assumed upon treatment discontinuation, which in turn was assumed to occur with transitions to moderate/severe AD, the company felt that this was sufficiently addressed. The EAG considers it questionable whether the relative effectiveness estimated from the 18 months observations in Clarity AD are reflective of treatment effect for the whole model time horizon, as the patient population changes over time. However, since no alternative data are available, the only available option is to explore the impact of treatment effect waning scenarios, and the EAG recommends that this be done, especially given the recommendations of the NICE HTA lab on the subject: *"In these circumstances, it is useful to explore alternative modelling scenarios, changing key assumptions about the long-term treatment effects that underpin extrapolations and assessing their impact on estimates of cost effectiveness."*[39]
In addition, the EAG notes that the lecanemab treatment effect was still assumed for patients that were off-treatment in the MCI due to AD and mild AD health states (both for institutionalised and community-dwelling patients). This could be justified given that these health states were predominantly populated through all-cause discontinuation and that the lecanemab treatment effect (i.e., transition probabilities for the lecanemab arm) was potentially calculated also including patients that had discontinued treatment. However, patients who did not attend the study visit at month 18 were excluded from the calculation of transition probabilities. In addition, the EAG is concerned that the model also includes this treatment effect beyond the 18 months observed trial period. This means that the model currently assumes a long-term treatment effect for patients that are off-treatment in the MCI due to AD and mild AD health states in the model. The EAG considers this to potentially add substantial bias. Use of the ITT population as opposed to the population of those who did not discontinue reduces the bias in the short term i.e. during the period over which discontinuation has been observed: in a sense the overestimation for those off treatment might be compensated for by the underestimation for those on treatment. However, it does not fully address the bias of assuming no reduction in treatment effect once discontinued beyond 18 months since more patients will have discontinued than observed in the trial. The EAG changes this in the base-case, instead assuming no treatment effect in patients off-treatment in MCI and mild AD health states and is interested in further justification for this modelling choice.

d) Mortality rates related to AD were based on hazard ratios versus cognitively normal individuals as reported in Crowell et al, which was identified by hand search and reported hazard ratios from the Uniform Data Set of the NACC database.[37] The model in Crowell et al. estimated a decreased risk of death in the MCI due to AD subgroup when compared with the cognitively normal group. In clarification question B9.e, the company was asked why the mortality rates have not been informed by Potashman et al. annual transition probabilities to death from each health state.[33] In their response, the company clarified that mortality rates in Potashman et al. have been expressed as a single probability of death based on current health state and did not

vary over time nor accounted for sex, which contradicts the expectation of increased mortality with age independently of disease progression. Therefore, it was deemed inappropriate for extrapolation over lifetime. In the company's scenario analysis using the transitions to death based on Potashman et al. in which the risk of death was constant, the ICER substantially increased by [redacted] compared with the corrected base-case PAS ICER. The EAG considers that the company's arguments against using mortality estimates by Potashman et al. in the base-case are valid, but explores this in a scenario because this improves the consistency with published models (see Section 5.4 for further detail).
The EAG further questioned the plausibility of assuming a decreased risk of mortality in the MCI due to AD subgroup in clarification question B14.b. The company explained that Crowell et al. acknowledge in their paper that relative mortality for the MCI due to AD health state compared with cognitively normal participants may have been underestimated, due to the more restrictive eligibility criteria for including people in the AD cohort compared with the cognitively normal arm of their study.[37] After controlling confounding factors and disease progression over time, Crowell et al. found no increase in mortality associated with MCI due to AD. The EAG consulted a clinical expert who considered Crowell et al. appropriate as a source for mortality estimates and also stated that *"this shows no greater mortality than in the general population for people with MCI due to AD"*. The company scenario analysis that assumed a mortality hazard ratio of 1.0 instead of 0.63 in the MCI due to AD health state led to an increase of [redacted] compared with the corrected base-case PAS ICER. The EAG considered it more appropriate to use mortality estimates in line with the general population and used this scenario in its base-case.

e) The EAG is unsure whether treatment discontinuation is appropriately captured in the company's model. First, all-cause discontinuation is assumed throughout the model horizon even though it was based on Clarity AD and therefore it is unclear whether this is appropriate beyond 18 months. Since the majority of patients discontinued because of AEs and withdrawal of consent it could be questionable whether the discontinuation rate stays constant over time during and after the trial. Especially when stopping rules are also used, there is a risk of double-counting of treatment discontinuation in the model. The EAG therefore recommends exploring a drop in the rate of all-cause discontinuation after 18 months of the model time horizon, and, in a scenario, disables all-cause discontinuation after 18 months.
The company's severity-based stopping rule is not how treatment is envisioned for use in clinical practice (as of yet), as the company continue to explore appropriate stopping rules. Meanwhile,
[redacted]
. According to the EAG clinical expert, a stopping rule with progression to moderate AD may be appropriate but *"How this is operationalised may be problematic given that CDR-SB is not currently used in clinical practice."* A severity-based stopping rule is also not in line with Clarity AD. In addition, there may be double-counting when the severity-based stopping rule is used in addition to all-cause discontinuation. In the absence of an agreed upon definitive stopping rule, and for the above reasons, the EAG removes the severity-based stopping rule in its base-case. A scenario with the stopping rule in place is also performed, as well as one with the severity-based stopping rule and all-cause discontinuation together.

To justify the assumption that patients would stop treatment upon institutionalisation, the company stated in their response to question B12a that they sought UK clinical expert opinion in this matter. One expert stated that the number of exceptions to stopping treatment upon institutionalisation would be "extremely small", a second expert stated it is very rare for patients with mild AD to enter institutional care and the third expert stated that where the patient lives is less important than AD severity. The company also argued that Alzheimer's Research UK (ARUK) stated that patients approaching the need for care facility admission would no longer meet the eligibility criteria for lecanemab. The EAG clinical expert considered that *"the exceptional patients with mild dementia who are institutionalised should not automatically have their treatment discontinued".* The EAG notes that relaxing this institutionalisation-based stopping rule increases the PAS ICER by approximately [redacted]. In summary, there remains uncertainty about whether patients do and should discontinue treatment upon institutionalisation, and this is explored in an EAG scenario where the institutionalisation-based stopping rule is disabled.

f) The EAG questioned the generalisability of Knapp et al. 2016 and Belger 2019 populations for the institutionalisation rates used in the model, especially because these studies were performed in populations that were not Aβ positive.[35, 36] The company explained that both Knapp et al. 2016 and Belger et al. 2019 reported data from the UK. Knapp et al. 2016, which was used in the base-case, analysed observational data for mental health clinical records for participants with AD with data linkage to UK Hospital Episode Statistics (HES), while Belger et al. 2019 was used in scenario analysis as it included patients outside of the UK. The company considered both studies appropriate in comparison to the non-UK based studies with confirmed Aβ pathology. The EAG notes the uncertainty around using institutionalisation rates from a population that is not Aβ confirmed.

4.2.7 Adverse events

The main source of evidence on treatment AEs used for intervention and comparators is the Clarity AD trial. In Clarity AD, AEs were graded on a three-point scale of mild, moderate, and severe, with the exception of infusion-related reactions which were graded based on the CTCAE. Adverse events were included in the analysis based on the following criteria:

- Treatment-related incidence of grade 3+ AEs occurring in ≥5% of patients in either treatment arm.
- ARIA-E, ARIA-H, and infusion-related reactions, irrespective of incidence and severity, as these were considered AEs of special interest.

No grade 3+ AEs occurred in ≥5% patients and therefore, only AEs of special interest were incorporated. Adverse events were modelled by severity grade, rather than presence of symptoms, to reflect the associated appropriate use recommendations reported by Cummings et al.[40] The company used treatment-emergent rates of isolated ARIA-H and justified this by stating this was to avoid double counting, provided that ARIA-H can occur concurrently with ARIA-E. Infusion-related reactions were assumed to be 0% for SoC. Adverse event management for the included AEs were derived from the lecanemab appropriate use recommendations in the USA (CS Table 58),[40] and supplemented by UK clinical experts.

EAG comment: The main concerns of the EAG relate to: a) exclusion of AEs associated with lumbar puncture testing, b) inclusion criteria for AEs, and c). utilised prevalence rates for ARIA-H.

a) Costs for (lumbar puncture) testing were included in the CS; however, the impact of related AE costs and effects were not considered. Baldaranov et al. 2022 assessed the impact of lumbar puncture CSF testing on AEs.[41] The study identified 227 testing-related AEs. Provided that treatment with lecanemab is contingent on the confirmation of Aβ pathology, the impact of testing AEs on costs and HRQoL should be incorporated into the economic model for all individuals that would otherwise not have been tested. This is particularly important provided that the majority of diagnostic testing is carried out with lumbar puncture. The inclusion of costs and effects for Aβ pathology testing is further discussed in key issue 1.
b) In the CS, only grade 3+ AEs that occurred in ≥5% of patients, and AEs of special interest, were included in the economic model. Clarification question B16 requested justification for excluding lower grade AEs and for the company to provide a full overview of AEs and frequencies from Clarity AD, separated by severity/grade. In response, the company suggest AEs below grade 3 are generally not included in CEA due to their limited cost and HRQoL impact. Further, no overview of individual TEAEs was provided due to over 100 being recorded in Clarity AD. Instead, clarification response Table 64 provided an overview of total TEAEs, separated by severity. The prevalence of mild and moderate TEAEs (n(%)) was higher in the lecanemab arm (mild: [redacted]); moderate: [redacted]) than the placebo arm (mild: [redacted]; moderate: [redacted]). The EAG therefore notes that the exclusion of mild and moderate TEAEs is likely to favour the intervention. The EAG further requested a scenario analysis incorporating all grade 3+ AEs, all grade 2+ AEs of special interest (ARIA-E, ARIA-H, infusion-related reactions), and all grade 2+ AEs occurring in ≥5% of patients. The requested scenario was not provided. The company suggest that all AEs of special interest were already included. However, in the CS, the impact of AEs on HRQoL was assumed to be captured by the utility values derived from the trial (i.e., not explicitly modelled as it is questionable whether the trial utilities adequately capture the HRQoL impact of AEs), and the impact of grade 1 and 2 infusion-related reactions on costs was assumed to be 0, despite providing an overview of treatment for grade 2 management (CS table 58). The company further highlight that Clarity AD included >200 distinct (MedDRA preferred term) AEs which predominantly occurred in <1% of patients. To provide context, the company highlight that including a hypothetical AE with a cost per event of £500 with an incidence of 1% in the lecanemab arm would increase the list price ICER by [redacted]. The EAG recognise the minimal impact of each included grade 3 AE with such a low prevalence, however, maintain that, given the volume of AEs with such status, excluding the costs and impact on HRQoL of a large volume of grade 3 AEs potentially biases the results in favour of lecanemab. Failing to provide a full overview of AEs in Clarity AD, separated by severity for each treatment arm, makes deciphering the likely extent of the impact difficult.
c) Rates of isolated ARIA-H were used to avoid double-counting, given ARIA-H can occur concurrently with ARIA-E. Treatment-emergent rates were used given the natural occurrence of ARIA-H in AD patients. The EAG requested an updated economic analysis including the associated rates for all AEs of special interest. In response, the company suggest that, given ARIA-E, ARIA-H, and infusion-related reactions were included, the CS is already aligned with this request. Given the response, the request was seemingly misunderstood. Rates of overall (isolated) ARIA-H were 9.0% (7.8%) for the placebo arm and 17.3% (8.9%) for the lecanemab arm. The plausibility of using isolated rates of ARIA-H, rather than overall rates, as well as the extent of the impact this had on model outcomes was unclear to the EAG. The clinical expert

consulted by the EAG suggested that ARIA-H and ARIA-E are often concurrent, with management for asymptomatic cases, accounting for the majority of cases, being similar regardless of whether ARIA-H and ARIA-E occur concurrently or in isolation. The EAG therefore recognises that using overall rates for both ARIA-H and ARIA-E would risk double-counting for asymptomatic management. However, the EAG notes that the current approach is likely to miss differences in management for symptomatic ARIA where AE management may differ between ARIA-H and ARIA-E. Utilising isolated rates of ARIA-H is therefore likely to underestimate the costs for lecanemab, although the EAG recognise the impact on costs is likely to be small. The consulted clinical expert also highlighted that the choice to use overall ARIA-E and isolated ARIA-H, rather than overall ARIA-H and isolated ARIA-E, is likely to have an impact, as discussed in Section 4.2.8.

4.2.8 Health-related quality of life

The utility values were estimated for the following health states, all stratified by care setting (community versus institution): MCI due to AD, mild AD, moderate AD, and severe AD. Caregiver HRQoL was included as utility decrements to patient values.

Clarity AD measured patient HRQoL using EQ-5D-5L and Quality of life in Alzheimer's disease (QOL-AD) at baseline and every six months. The patient's study partner also served as the patient's proxy, completing the EQ-5D-5L and QOL-AD on the patient's behalf. In addition, study partners completed a self-assessment of EQ-5D-5L and Zarit's Burden Interview (ZBI).

4.2.8.1 Health-related quality of life data identified in the review

According to the CS, the SLR identified nineteen UK-specific studies. Of these, fourteen reported patient-reported utilities, with thirteen reporting patient-by-proxy EQ-5D values, and eight studies reporting caregiver self-reported utilities (of which, three included EQ-5D utilities by various dementia severity levels). Six of the 19 studies included EQ-5D utilities for UK patients with various dementia severity levels. Further, one meta-analysis was identified, which analysed EQ-5D utility estimates from 48 studies across multiple countries. One study[1] reported disparities in patient utilities between community and institutional (specifically, residential care home settings) care using a regression model. However, this study did not distinguish between disease severity levels.

4.2.8.2 Health state utilities used in the model

Patient utilities for the MCI due to AD and mild AD health states are derived from Clarity AD. According to the CS, Clarity AD did not contain sufficient observations to inform health state utilities for moderate AD or severe AD health states, and did not contain data regarding the institutional care setting. Therefore, published studies were utilised for the moderate AD and severe AD health states in the community setting, and for all health states in the institutional care setting. To preserve differences between health states when using published studies, decrements were calculated for each set of published utilities relative to the previous health states. These were applied additively to the associated utility from clarity AD. In the economic analysis, only published studies reporting health state utilities for mild, moderate, and severe AD were thus included. To align with the model and NICE reference case, studies reporting EQ-5D-3L utilities from exclusively UK respondents, stratified by care setting, were preferred. In a UK HTA advisory board, one clinician stated it would be appropriate to switch from patient-reported utilities to caregiver proxy utilities at moderate or severe AD health states, whilst another clinician stated that proxy values should be used for all stages of dementia. Following this, the company utilised patient-reported utilities for MCI due to AD and mild AD health states, with proxy-reported estimates being utilised for moderate and severe AD health states.

Caregiver utilities are also included in the economic analysis, applied as utility decrements in mild, moderate and severe AD health states. These are applied to caregiver utilities for MCI due to AD from Clarity AD. Within community care, caregiver utilities were derived from Clarity AD for the MCI due to AD and mild AD health states. For the moderate AD and severe AD health states, values were derived from literature identified in the SLR.[42] The chosen study was selected over others due to face validity (one study[43] reported higher utility values for severe versus moderate AD; one study[1] reported higher utility estimates in the severe AD than the age- and sex-matched general population) and the inclusion of UK participants. For institutional care, the coefficient from the caregiver EQ-5D-3L regression model in Farina et al. was applied additively to the community care utilities in all health states.[1]

A summary of health state utility values used in the CEA is provided in Table 4.14. Note, these values relate to patient utilities in the community setting. Caregiver utilities and the impact of institutional settings are applied additively through a disutility approach.

Table 4.14: Health state utility values (community setting)

Health state	Utility value (Lecanemab)	Utility value (SoC)	Reference	Justification
MCI due to AD	[redacted]	[redacted]	Clarity AD (Patient-reported)	
Mild AD	[redacted]	[redacted]	Clarity AD (Patient-reported)	
Moderate AD	0.686	0.674	Farina et al. 2020 (Caregiver as proxy) *	Insufficient observations in Clarity AD. Farina et al. chosen as EQ-5D-3L proxy estimates for all AD health states reported with UK participants.
Severe AD	0.586	0.574	Farina et al. 2020 (Caregiver as proxy)*	Insufficient observations in Clarity AD. Farina et al. chosen as EQ-5D-3L proxy estimates for all AD health states reported with UK participants.

Based on CS Model; Farina et al. 2020[1]
*Decrement between health state values derived from Farina et al. (2020) and applied to mild AD health state values.
AD = Alzheimer's disease; CS = company submission; EQ-5D-3L = European Quality of Life-5 Dimensions-3 Level; MCI = mild cognitive impairment; SoC = standard of care; UK = United Kingdom

4.2.8.3 Disutility values

To derive utility values for **institutional settings**, decrements were derived from Farina et al. 2020[1] and added to community utility values to derive utilities for corresponding health states. A decrement of 0.01 was applied to the MCI due to AD and mild AD health states, based on patient-reported values. A

decrement of 0.16 was applied to moderate and severe health states, derived from caregivers as proxy values.

To incorporate the impact on caregivers, **caregiver disutilities** were derived from Black et al. 2018[42] and applied to health state utility values. Disutilities applied, relative to the previous health state, were as follows: MCI due to AD: 0.00; Mild AD: 0.02; Moderate AD: 0.03; Severe AD: 0.02.

The impact of **adverse events** on HRQoL was assumed to be captured and therefore no disutilities were incorporated.

EAG comment: The main concerns of the EAG relate to: a) the method for estimating and applying utility values, b) use of treatment-dependent utilities within the same health state, c) disutility applied to caregiver HRQoL for patient institutionalisation, d) utility values higher than general population values, e) exclusion of AE disutilities, and f) use of caregiver proxy values to inform patient HRQoL for moderate AD and severe AD health states.

a) To estimate health state utility values for the MCI due to AD and mild AD health states from Clarity AD, the mean utility index scores were calculated by corresponding health state. That is, the mean EQ-5D value was calculated across all (post-)baseline observations. This was done separately per treatment arm. Further, no imputation of missing data was conducted. The current approach does not take into consideration within/between patient variability, which may result in utility estimates that do not fully capture the full range of health state utility values. The approach also ignores potential confounding variables that may influence health state utilities. Additionally, aggregating results across time points fails to capture any changes to health state utility values over time, potentially oversimplifying results. The EAG question the approach taken to derive health state utilities and propose the use of an alternative approach (i.e., mixed effects model) to account for potential confounding variables and to handle variability within and between patients over time. Further, justification should be provided for the decision to not perform missing data imputation.
   When applying utility values within the economic model, utility decrements are additively applied to base health state values. Use of a multiplicative approach, using adjusted baselines, is currently recommended by NICE (NICE Decision Support Unit (DSU) TSD 12) and the EAG would thus prefer that the company provided a multiplicative approach to utility calculations.
b) CS Table 45 provides a summary of treatment-dependant EQ-5D utility index scores by health state from Clarity AD (using CDR-SB score). Modelled utilities for lecanemab are consistently higher than the placebo utilities within the same health state. In response to CQ B17, the company justify treatment-dependent utilities through suggesting that the difference may be attributable to differences in disease severity within a given health state. For example, CDR-SB score of 5 and score of 9 would both be classified as mild AD despite the former potentially being expected to have more favourable utilities. Clarification response Table 30 highlights that the mean CDR-SB (baseline [18-months]) score is slightly lower in the lecanemab arm ([redacted] [redacted]) than the placebo arm ([redacted] [redacted]) for the MCI due to AD health state. Indeed, CDR-SB scores are also lower for lecanemab ([redacted] [redacted]) than for placebo ([redacted] [redacted]) in the mild AD health state. However, the company concede that detecting differences between CDR-SB scores in HRQoL within health states is limited by the lack of statistical power to detect them. The EAG requested a scenario analysis utilising treatment-independent utility values for all health states. The scenario resulted in an increase in the PAS ICER to [redacted], constituting a [redacted] increase. In combination with the uncertainty in the utility estimation approach (see EAG comment a), the EAG adopted treatment-independent utilities within its base-case.

c) To capture the impact of patient institutionalisation on caregiver HRQoL, a coefficient of -0.09 was additively applied to the community care utilities in all health states.[1] This suggests that patient institutionalisation would negatively impact caregiver utility. Conversely, Van Hezik-Wester et al[43] and Farina et al[1] report higher caregiver utilities for severe AD versus moderate AD, which may be explained by patient institutionalisation having a utility increment (i.e., as a result of caregiving duties being reduced/taken over by an institution). Clarification question B18 requested elaboration on the impact of patient institutionalisation on caregiver HRQoL, providing evidence to justify the modelled decrement. The company highlight that, in Van Hezik-Wester et al, Table 5 also shows a mean decrease in caregiver utility for institutionalised patients (0.758) compared with community-dwelling patients (0.832). However, this value does not account for disease severity, which may be the driving factor for the lower caregiver utility. Further, the company highlight that, despite Farina et al[1] reporting higher carer QoL for severe AD compared to moderate AD, the study also reported a utility decrement of -0.09 for caregivers when a patient is institutionalised. However, it is unclear whether there is a substantial correlation between severity and care setting variables (no interaction terms provided), leading to multi-collinearity, destabilising coefficient estimates. In addition, the clinical expert consulted by the EAG suggested that a reduction in caregiver utility following the patient moving into an institutional setting is not usual, and highlights a prospective cohort study, conducted in eight countries including England, finds no significant change in EQ-5D-3L or European Quality of Life – visual analogue scale (EQ-VAS) utilities before and after institutionalisation[44]. In conclusion, the effect of institutionalisation on caregiver utilities is unclear and the EAG disables the utility decrement in its base case.

d) The current approach to estimating utility values for the MCI due to AD and mild AD health states resulted in utility values that are higher than the UK age and gender matched general population utilities, calling into question the face validity of the approach. Following CQ B17, the company accept that capping utility values at the age and gender matched values may provide more face validity. The company provided a scenario analysis, resulting in an increase in the PAS ICER to [redacted]. Provided the uncertainty surrounding the approach to estimate utility values for the MCI due to AD and mild AD health states, and that the subsequent moderate and severe health state utility values are dependent on these, the EAG is uncertain whether providing a cap is the best option and has therefore not implemented this in its base-case. However, the EAG considers the utility values higher than the UK age and gender matched utilities for the general population to be questionable.

e) No AE disutilities were modelled. This was justified in the CS under the assumption that the impact of AEs would inherently be captured within utility estimates for lecanemab in Clarity AD. However, HRQoL measures were only administered every six months within the trial. As such, the EAG questions whether the impact of AEs is truly captured. Hampel et al. 2023[45] report symptomatic ARIA-E cases resolving within 3-4 months or upon treatment cessation. This further suggests the impact on HRQoL is unlikely to be sufficiently captured. Clarification question B15 requested discussion regarding the plausibility of excluding AE disutilities and requested a scenario analysis whereby AE disutilities were incorporated into utility values. In response, the company acknowledge that, given the frequency of data collection, the full impact of AEs on HRQoL may not be captured. However, they suggest that applying disutilities to health state utilities would likely result in double-counting. This is questionable given that utility values were higher for lecanemab as compared to the placebo arm in Clarity AD, despite the higher prevalence of adverse events. The scenario analysis was conducted by the company, utilising proxy AE disutility values for ARIA-H (transient ischemic attack, Meckley et al. 2010[46]), ARIA-E (pooled analysis of chronic condition disutility, Sullivan et al. 2006[47]), and

infusion-related reaction (injection-related attributes for type II diabetes, Boye et al. 2011[48]). The clinical expert consulted by the EAG suggested the chosen proxies for ARIA disutilities were reasonable. It is unclear to the EAG whether the choice of proxy for infusion-related reactions was reasonable. The company assumed AE durations to be six days for ARIA, and three hours for infusion-related reactions, based on clinical expert opinions. The chosen duration for ARIA events was particularly low with the EAG-consulted clinical expert highlighting that stabilisation or resolution typically takes 4-12 weeks. The clinical expert further suggested that, while most infusion-related reactions associated with lecanemab are brief and of low severity, grade 3+ infusion-related reactions would imply severe and prolonged reactions, potentially requiring hospitalisation for monitoring and life-threatening consequences and need for prophylactic treatment if further lecanemab dosing is considered. Therefore, the duration of infusion-related reactions is also likely to underestimate the impact on HRQoL. The same disutility was applied by the company for grade 3 and 4 AEs. Disutilities were only applied to grade 3+ AEs. The following disutility values were applied: 0.1 for ARIA-H, 0.0266 for ARIA-E, 0.01 for infusion-related reactions. The resulting PAS ICER was [redacted]. Given the severity of grade 3+ infusion-related reactions, the EAG-consulted clinical expert suggests the utilised disutility is likely to underestimate the impact on HRQoL. Further, for ARIA-E and ARIA-H, the expert suggests that applying a disutility to grade 1 and 2 AEs, in addition to a higher value for grade 3+ ARIA AEs, would be appropriate. Therefore, it is likely that the scenario analysis provided by the company underestimates the impact of AEs on HRQoL and cost effectiveness results. The EAG incorporated the company's scenario into its base-case but notes that the impact of AEs is unlikely to be fully captured.

f) Utility estimates derived from caregiver proxies were utilised for the moderate AD and severe AD health states. In the company's HTA advisory board meeting, one clinician stated that it would be appropriate to switch to caregiver proxy reported utility values at moderate or severe AD, with another clinician stating that proxy values should be used for all stages of dementia. Other clinicians did not specify when would be best to switch. The company's selection to switch at the moderate AD health state was justified through wanting to utilise patient-reported values so as not to deviate from the NICE reference case. Further, the company considered evidence from a meta-analysis (Landeiro et al. 2020) which found large differences between self-reported and proxy utility values, with clear divergence at mild to moderate AD and increasing through moderate and severe AD.[49] Clarification question B19 requested a scenario analysis utilising patient-reported utilities for the moderate AD health states. The company provided results to the requested scenario analysis, utilising patient-reported utility values for all health states apart from the severe AD health state, which utilised proxy values. As there were insufficient observations in Clarity AD to reliably inform health state utilities for moderate AD (N=[redacted] for lecanemab, N=[redacted] for placebo), the company informed utilities for the moderate AD health state from Farina et al[1] (mean [standard deviation, SD]: 0.8 [0.2]). This resulted in a decrease in the PAS ICER to [redacted]. The clinical expert consulted by the EAG highlighted that nearly all patients with MCI and mild dementia due to AD understand and seem able to report reliably (although report consistently higher ratings than proxies). Further, a significant proportion of those with moderate, and nearly all patients with severe, dementia due to AD lack understanding and are therefore unlikely to report reliably. As such, proxy-reported values are best for both moderate and severe AD, with an argument to be made to utilise proxy values for all health states for consistency reasons. The EAG therefore accepts the company's justification for utilising proxy utilities for the moderate and severe AD health states and adopts the same approach in its base-case.

4.2.9 Resources and costs

The cost categories included in the model were treatment acquisition costs, administration costs, monitoring costs, diagnostic testing costs, symptomatic treatment costs, adverse events costs, and direct medical and direct non-medical care costs (i.e., social care costs met by local authorities).

Unit prices were based on the NHS reference prices, British National Formulary (BNF) and Personal Social Services Research Unit (PSSRU).

4.2.9.1 Resource use and costs data identified in the review

According to the CS, the SLR identified 26 studies reporting UK relevant resource use and cost information. One additional paper was identified in a hand search that was conducted to identify additional sources of health state costs for the model reporting direct and non-direct medical costs classified according to severity and setting for UK patients with dementia due to AD. None of the identified studies were directly used to inform the economic model. However, costs in the study by Paquete et al[50] were informed by the Alzheimer's Society report and a US study by Robinson et al[51]. The Alzheimer's Society report and a ratio of costs between health states from Robinson et al were used in the economic model to inform health state costs, direct medical and non-medical costs, and unpaid care costs.

4.2.9.2 Treatment costs

4.2.9.2.1 Lecanemab

Lecanemab is offered at list prices of [redacted] and [redacted] per 200 mg and 500 mg vial ([redacted] and [redacted] including PAS), respectively. The lecanemab dosing regimen is 10 mg/kg IV infusion once every two weeks (i.e., 2.17 doses per month) [redacted]. Lowest cost combinations of vials were calculated based on the weight distribution of the European ITT population (n=390) of Clarity AD, allowing for the incorporation of vial wastage. The monthly lecanemab acquisition cost including non-compliance (mean compliance informed by Clarity AD was [redacted]) is [redacted].

Lecanemab is administered via a one-hour IV infusion. As there is currently no specific NHS reference cost for the IV infusion of a DMT for AD, the administration cost for lecanemab was assumed to be the average cost of a simple parenteral chemotherapy infusion as reported in the NHS reference costs 2021/22 (£207.59 per infusion).

Treatment with lecanemab requires MRI monitoring due to the risk of ARIA. Based on the average of the responses of four UK clinical experts,[52] 3.88 MRIs are modelled in year 1 and 1.13 in the years thereafter. The unit cost of an MRI was sourced from NHS reference costs.[53]

4.2.9.2.2 Comparators

The proportion of patients receiving symptomatic treatments (AChEis [donepezil, rivastigmine, and galantamine] and memantine) differs by health state and was informed by Clarity AD, estimated as the proportion of time for which symptomatic treatment was received out of the total time spent by patients whilst in each health state (CS Table 52). The monthly weighted cost of AChEis was calculated using the proportion of patients that received donepezil, rivastigmine, or galantamine, respectively, in Clarity AD. The unit cost of all symptomatic drugs was sourced from the electronic market information tool (eMIT) 2022.[54] No administration costs were modelled, as all symptomatic treatments are administered orally.

Table 4.15: Monthly drug acquisition costs for lecanemab and symptomatic treatment

Health state	Lecanemab (including non-compliance)	Symptomatic treatment
MCI due to AD	[redacted]	£1.19
Mild AD	[redacted]	£1.60
Moderate AD	[redacted]	£1.82
Severe AD	[redacted]	£2.11

Based on CS Section B.3.5.2[2]
AD = Alzheimer's disease; CS = company submission; MCI = mild cognitive impairment

4.2.9.3 Diagnostic costs

As treatment with lecanemab is conditional upon confirmation of Aβ pathology (measured by amyloid PET or CSF testing), the company included the costs of diagnostic testing in their base-case analysis for patients treated with lecanemab. Experts in the UK HTA advisory board agreed that 90% of diagnoses would be via CSF testing, due to PET capacity constraints and scalability of CSF testing. These proportions were applied to the unit costs to calculate the mean diagnostic cost per patient (CS Table 55).

4.2.9.4 Health state costs

Health state costs included in the company's base-case are direct medical (i.e., healthcare costs such as primary, community and secondary care visits) and non-medical costs (i.e., social care costs such as residential care costs and home-based community care).

4.2.9.4.1 Direct medical costs

Annual direct medical costs for each health state are presented in Table 4.16. As costs for MCI were not reported in any of the studies identified in the SLR, the cost for MCI due to AD was calculated as 85% of the cost for mild AD, as per the ratio of health state costs for the US reported by Robinson et al.[51] The annual costs are adjusted to monthly values to align with the model cycle length.

Table 4.16: Annual direct medical care costs

Health state	Community cost	Institution cost	Reference
MCI due to AD*	£2,704.75	£4,428.28	Alzheimer's Society 2014[55]
Mild AD	£3,182.06	£5,209.74	
Moderate AD	£3,117.29	£10,916.87	
Severe AD	£13,022.05	£10,050.50	

Based on CS Table 56[2]
AD = Alzheimer's disease; CS = company submission; MCI = mild cognitive impairment

4.2.9.4.2 Direct non-medical costs

Annual direct non-medical costs for each health state are presented in Table 4.17. Costs for MCI due to AD in the community were estimated using the same method as described for direct medical care costs. As direct non-medical costs in the institutional care setting are similar across AD disease states, costs in the MCI due to AD health state were assumed equal to the mild AD state. The annual costs were converted to monthly costs to align with the model cycle length.

Table 4.17: Health state costs

Health state	Community cost	Institution cost	Reference
MCI due to AD*	£1,949.42	£28,613.11	Alzheimer's Society 2014[55]
Mild AD	£3,610.04	£28,613.11	
Moderate AD	£8,989.82	£29,744.36	
Severe AD	£11,938.23	£29,928.27	
Based on CS Table 57[2] AD = Alzheimer's disease; CS = company submission; MCI = mild cognitive impairment			

4.2.9.5 Adverse event costs

In absence of published UK guidelines for the management of ARIA-E, ARIA-H, and infusion-related reactions, the associated resource use and costs were adapted from lecanemab appropriate use recommendations in the US reported by Cummings et al,[40] supplemented with UK clinical expert opinion (CS Table 58). Unit costs of antihistamine, paracetamol, oral dexamethasone, prednisolone and methylprednisolone were obtained from the BNF.[56] It was assumed that [redacted]% of patients experiencing serious-severe ARIA-E and [redacted]% of patients experiencing isolated ARIA-H would require hospitalisation based on Clarity AD.[25] The unit cost of a hospitalisation for ARIA was assumed to be an average of Non-Elective Inpatient – Long Stay: AA23C-G, Haemorrhagic Cerebrovascular Disorders across CC scores from the NHS reference costs 2021-22[53] (CS Table 59).

4.2.9.6 Caregiving costs

As unpaid care accounts for 40% of the total costs of dementia care in the UK, unpaid care costs were included as a scenario analysis. The costs of unpaid care were taken from the Alzheimer's Society 2014 study and inflated to 2022 prices using the PSSRU inflation indices[55, 57] (CS Table 60).

EAG comment: The main concerns of the EAG relate to: a) cost and resource use disparities between the company's economic model and the NHS England Alzheimer's MCI model, b) diagnostic testing costs for confirmation of Aβ pathology included for patients treated with lecanemab only, c) the inclusion of health state costs outside the NHS and PSS perspective on costs, d) cost implications related to the mismatch between the modelling of established clinical management and UK clinical practice.

a) The EAG compared the cost and resource use included in the company's economic model and the NHS England Alzheimer's MCI model. A number of discrepancies were identified as highlighted in Table 4.18 below, including differences in unit costs, MRI safety monitoring, Aβ and *ApoE4* testing, GP visits, quarterly outpatient reviews, and referral to local services.
   1) The EAG adopted the IV infusion administration, lumbar puncture and PET-CT unit costs from the NHS England Alzheimer's MCI model in its base-case.
   2) As patients treated with lecanemab have an increased risk of ARIA, the draft SmPC states that [redacted] The NHS England Alzheimer's MCI model included MRIs in intervals of 13 weeks (corresponding to four MRIs in the first year of treatment). It was, however, unclear how many MRIs were obtained in the years thereafter. The EAGs clinical expert referred to the lecanemab appropriate use recommendations in the US reported by Cummings et al,[40] which also suggests four MRIs in the first year and at any time if symptoms suggestive of ARIA occur (and monthly until it resolves or stabilises). The EAGs clinical expert further stated that the recommendations do not consider beyond the

first year, but that a 6-monthly MRI is probably appropriate. The company modelled averages of 3.88 MRIs in the first year and 1.13 MRIs in the years thereafter based on UK clinical expert input at a UK HTA advisory board. In response to clarification, the company stated that the appropriate MRI monitoring schedule for Clarity AD was determined based on the frequency, timing, and severity of ARIA observed in Study 201. This resulted in MRI monitoring taking place at week 9, week 13, month 6, month 12, and month 18. The modelled average of 3.88 MRIs in the first year of the company's model is slightly lower than the four MRIs as estimated in the NHS England Alzheimer's MCI model and the EAG's clinical expert comment. The additional average of 1.13 MRIs in the years thereafter is also lower than the two MRIs per year that are expected by the EAGs clinical expert. Next to that, [redacted] of the patients treated with lecanemab in Clarity AD were *ApoE4* carriers, which are, as indicated by Table 13 of the Clarity AD CSR, at a higher risk of ARIA than non-carriers. In response to clarification question A23, the company stated that [redacted] of patients in the Clarity AD lecanemab arm had their treatment suspended due to ARIA, of which [redacted] experienced more than one suspension of treatment due to ARIA. The mean treatment suspension duration due to ARIA was [redacted] weeks in the lecanemab arm and the mean number of required additional MRIs was [redacted]. The company further argued that the additional MRI scans (and the duration, where relevant), that are required before resumption of treatment, in patients in whom lecanemab treatment has been suspended due to ARIA, are reflected in AE management costs in the model. The EAG aligned its base-case with the NHS England Alzheimer's MCI model and the EAGs clinical expert comments and included four MRIs in the first year and two MRIs in every year thereafter for the modelling of lecanemab safety monitoring.

3) For Aβ pathology testing, the company assumed that 90% of diagnoses would be via CSF testing and the remaining 10% via PET-CT (based on clinical expert opinion during the UK HTA advisory board), while the NHS England Alzheimer's MCI model assumed this ratio would be 85%:15%. The EAGs clinical expert considered the company's 90%:10% assumption to be reasonable and therefore no further changes were made in the EAG's base-case.
4) Contrary to the NHS England Alzheimer's MCI model, the company did not include costs for GP visits, quarterly outpatients' reviews, *ApoE4* testing and referral to local services in their economic model. Although the NHS England Alzheimer's MCI model assumes three GP visits per patient and four quarterly outpatient reviews per year, there is no mention of GP visits nor quarterly outpatient reviews in the CS. Regarding *ApoE4* testing, the company argued in response to clarification that this is not routinely conducted in UK clinical practice and is not funded by NHS England, but that it is under consideration. The company's clinical experts argued that if *ApoE4* testing becomes a requirement, this would be offered to all patients considered eligible for treatment with lecanemab but it would not be mandatory due to the genetic implications. However, one expert added it should be decoupled from starting therapy and *ApoE4* testing should be for everyone as part of standard clinical practice. The EAG's clinical expert would expect most people (90%+) to receive *ApoE4* testing, even if it is not mandated in the marketing authorisation. A scenario analysis including the costs of *ApoE4* testing was requested, but the company did not provide this analysis. Given that *ApoE4* testing may be recommended prior to treatment initiation (to determine the risk of developing ARIA), the EAG performed a scenario in which the cost of *ApoE4* testing and related outpatient visits was included (applied to all patients treated with lecanemab, and counselling costs included for 50% of homozygous patients (30%). Regarding patient referral to local services, in response to clarification, the

company stated that following a dementia diagnosis, NHS dementia diagnosis guidance indicates that patients should continue to have check-ups in primary care for ongoing dementia assessment. As such, the costs of referral to local services for people that are not Aβ positive would apply equally to lecanemab and SoC patients and hence would not be increased due to the introduction of lecanemab. The company therefore expects that the inclusion of such costs would not impact incremental costs and cost effectiveness. Despite the abovementioned arguments of the company, the EAG would like to see an updated economic model and scenario analysis including costs of GP visits, quarterly outpatients' reviews, *ApoE4* testing and referral to local services.

Table 4.18: cost and resource use comparison between the company's economic model and the NHS England Alzheimer's MCI model.

Cost/resource use	Company model	NHS England Alzheimer's MCI model
Unit cost lecanemab administration IV infusion per visit	£207.59	£565.00
Unit cost lumbar puncture	£295.80	£580.00
Unit cost PET-CT	£396.94	£1000.00
Aβ testing: ratio CSF:PET CT	90%:10%	85%:15%
MRI safety monitoring	Average of 3.88 MRIs in year 1 and 1.13 in years 2, 3, and 4	MRIs in intervals of 13 weeks
GP visit	Not included	3 visits (total cost of £75.00)
Quarterly outpatient review	Not included	Every 13 weeks (£350 each)
ApoE4 test	Not included	Unit cost of £250
		Outpatient appointment: unit cost of £200
		Counselling: unit cost of £350
Referral to local services (e.g., memory clinics)	Not included	Unit cost: £400

APoE4 = apolipoprotein E4; CSF = cerebrospinal fluid; GP = general practitioner; IV = intravenous; MCI = mild cognitive impairment; MRI = magnetic resonance imaging; NHS = National Health Service; PET-CT = positron emission tomography computed tomography

b) As treatment with lecanemab is conditional upon confirmation of Aβ pathology, the company included diagnostic testing costs in its base-case. However, testing costs were only included for patients treated with lecanemab, thus ignoring costs for testing patients subsequently deemed not to be eligible for lecanemab, as mentioned in Section 2.1. In line with the EAG request, in its clarification response the company provided a scenario analysis which incorporates diagnostic testing costs for all people eligible for screening into the costs for lecanemab. For this, the company used the screening failure rate for Aβ positivity of 28.80% from Clarity AD. Although the EAG adopted the company's scenario analysis including diagnostic testing costs for all people eligible for screening in its base-case, it preferred to use the screening failure rate

from the HTA lab for the calculation of the total diagnostic testing costs. Note that this does not include any potential harm to the health of those tested, as discussed in Section 2.1.

c) Health state costs in the CS included direct medical and non-medical costs, stratified by care setting (community/institution). It was unclear to the EAG what these costs exactly entailed and whether these were in line with the NHS and PSS perspective on costs in NICE's reference case. Therefore, further details and a clear overview of all included medical and non-medical costs were requested. The company responded that the direct medical and non-medical costs were taken from the Alzheimer's Society Dementia UK Update (2014),[55] in which the values constitute average healthcare costs per person with dementia based on data from a number of trials and other studies. Direct medical costs in the model refer to healthcare costs in the report, covering all primary, community, and secondary care services used. Direct non-medical costs refer to social care costs in the report, covering public and private costs of assessment and care management, residential care, and home-based community care. The EAG questions whether these social care costs are within the NHS and PSS perspective on costs. In response to clarification question B24, the company stated that the Alzheimer's Society report does not define what private costs are comprised of, nor what proportion of the reported costs are attributable to private care. The company acknowledged that it is therefore possible that the costs are not fully in line with the NICE reference case, but highlighted that it was not possible to estimate the proportion of costs from the Alzheimer's Society report that fall outside of the NICE reference case. The company conducted a scenario analysis assuming that 10% of health state costs are attributable to private care, which resulted in a minor increase of the ICER. Although the EAG agrees that private care costs should be excluded from the analysis, it considers the company's assumption that private care makes up 10% of health state cost not sufficiently justified. The Alzheimer's Society stated that two-thirds of the annual dementia costs are currently paid by people with dementia and their families, either in unpaid care or in paying for private social care,[58] indicating that the company may have underestimated the health state costs attributable to private care. Although the EAG acknowledges that assuming two-thirds of health state costs to be attributable to private care is likely an overestimation, given that the company's health state costs did not include unpaid care, an EAG scenario analysis was explored to assess the impact of this on the cost effectiveness results.

d) As commented on by the EAG in Section 4.2.4, AChEis and memantine are provided in all health states, which is inconsistent with NG97 stating that AChEis should be provided to mild AD (not MCI due to AD) and that memantine is an option for severe AD, or moderate AD ineligible for AChEis. In response to clarification question B22, the company conducted a scenario analysis with no pharmacological symptomatic treatments for patients in the MCI due to AD health state and no memantine usage for patients in the mild AD health state. This resulted in a very slight ICER decrease, indicating that the cost implications of this issue are negligible.

4.2.10 Severity

The company state that lecanemab does not meet the criteria for a severity weight based on the absolute and proportional quality-adjusted life year (QALY) shortfall methodology specified in the NICE manual. The company note the potential biases in absolute QALY shortfall against older populations, and in proportional QALY shortfall against chronic diseases.

EAG comment: The EAG confirms that criteria for severity modifiers are not met.

4.2.11 Uncertainty

The company described multiple sources of uncertainty:

- The chronic nature of AD means it can take many years for early AD patients to progress through the various stages of disease severity, with patients typically living for four to eight years following diagnosis, reaching 20 years in some cases. Key outcomes for the economic analysis, such as progression to more severe disease states, institutionalisation, and death, occur beyond the timeframe of a clinical trial such as Clarity AD for most patients.
- Data for patients with MCI due to AD are sparse and data to inform progression of AD patients with Aβ pathology (who are expected to progress at a higher rate than those without) are also sparse, as amyloid confirmation is not routine for current AD diagnoses. The company attempted to minimise the impact of uncertainty in the economic model by using published natural history data for patients with confirmed amyloid pathology identified via a SLR, with the caveat that these are not UK specific.
- Patient-reported HRQoL data are only suitable for less severe health states due to the substantial divergence between patient reported and proxy caregiver reported EQ-5D scores observed with increasing AD severity
- Long-term data for this new class of therapy are limited, with a possibility that the cumulative benefit of lecanemab may not be apparent to patients and family members until years after the intervention. The company considered that this was unavoidable, given the lack of feasibility of decade-long RCTs.

[redacted]

EAG comment: The EAG agrees with the areas of uncertainty outlined by the company and also broadly agrees with the efforts by the company to address uncertainty. The EAG has filled in the TRUST tool for identifying uncertainties based on their observations on the CS and company model to compile the remaining uncertainties and assess their potential impact.[59] The most important uncertainties were observed in treatment effectiveness and related to the health state occupation of the modelled starting population (potential bias); the estimation of transition probabilities (methodological uncertainty); mortality (potential bias); institutionalisation (unavailability); and lack of long-term relative effectiveness estimates (unavailability). For some of these uncertainties, the impact on cost effectiveness could be high. Uncertainties related to the decision problem include the generalisability of concomitant treatments and SoC to UK clinical practice. The impact of this is unknown. Some important model parameters were not based on SLRs but hand searches, but the EAG is reassured that overall, the best possible sources of evidence were identified and that the impact of this uncertainty is low. For AEs, there is lack of transparency as well as potential bias in how they are included in the model, and though the impact may be low, it might be worth exploring this further. Methodological uncertainty remains about the estimation of utility values derived from Clarity AD and the impact of this may be high.

In conclusion, there is significant uncertainty about various aspects in this appraisal and it may be possible to address some of this with further data collection, collection of expert opinion, and further analyses. Further data collection may help inform: long-term effectiveness of lecanemab (with the caveat that unanchored indirect treatment comparisons are prone to bias) and rates of institutionalisation. Collection of expert opinion may inform the health state occupation in the starting population and appropriateness of stopping rules. Further analyses may help address the methodological

uncertainty in the estimation of transition probabilities in the presence of competing risks and utilities, as well as assess the impact of inclusion of adverse events (with the duration also informed by experts).

5 COST EFFECTIVENESS RESULTS

5.1 Company's cost effectiveness results

The original CS base-case cost effectiveness results (probabilistic, superseded later by an updated CS base-case, see below) indicated that lecanemab is both more effective (incremental QALYs of [redacted]) and more costly (additional costs of [redacted]) than current care amounting to an ICER of [redacted] per QALY gained. [redacted]

Overall, the technology is modelled to affect QALYs by:

- Increased QALYs for lecanemab by increasing the number of patients staying at the MCI and community stage, through slower disease progression and treatment-dependent utilities (QALY gain [redacted]).
- Increased life years gained (LYG) for lecanemab through slower disease progression (LY increased by [redacted] compared with SoC).

Overall, the technology is modelled to affect costs by (see CS Appendix Table 58):

- Increased acquisition costs (additional costs of £[redacted] compared with SoC).
- Increased administration costs (additional costs of £[redacted] compared with SoC)
- Increased monitoring costs (additional costs of £[redacted] compared with SoC)
- Increased test costs (additional costs of £[redacted] compared with SoC)
- Costs saving in direct non-medical care costs in the institutional care (cost saving of £[redacted] compared with SoC)

Table 5.1: Base-case results QALYs – disaggregated

	SoC QALY (discounted)		Lecanemab QALY (discounted)		Incremental vs. SoC	
Health state	**Community**	**Institution**	**Community**	**Institution**	**Community**	**Institution**
MCI due to AD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mild AD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Moderate AD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Severe AD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Based on CS Appendix J1.2, Table 57[9]

AD = Alzheimer 's disease; CS = company submission; MCI = mild cognitive impairment; QALY = quality-adjusted life-year; SoC = standard of care

Table 5.2: Base-case results – aggregated

Technologies	Total			Incremental			ICER (per QALY)	NHB at £30,000
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs		
SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lecanemab	[redacted]	[redacted]	[redacted]					

Based on CS, Table 66[2]

Technologies	Total			Incremental			ICER (per QALY)	NHB at £30,000
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs		
CS = company submission; ICER = incremental cost effectiveness ratio; LYG = life years gained; NHB = net health benefit; QALY = quality-adjusted life-year; SoC = standard of care								

The company provided updated base-case results alongside their responses to the clarification letter, based on the updates in the economic model, which included the following:

- The company used transition probabilities that were informed directly by the probabilities reported in Potashman et al. in their updated economic model.[33] The original submission included transition probabilities derived from Potashman et al. as they were reported in Herring et al, which calculated an AD 'landing spot' distribution for patients leaving the MCI due to AD health state, requiring an additional calculation step that was not needed when using the probabilities directly from Potashman et al, according to the company.[34]
- The company updated the economic model using week-81 patient count data for health states using CDR-SB and global CDR (scenario analysis only). The original submission used week-79 patient count for the 0-18 months transitions. According to the company, the week-81 count is more reflective of the ITT FAS+ population, as some patients had their final visit more than one week later than the protocol specified.
- The company revised the health state costs in the economic model, incorporating corrected inputs for community and institution costs from the Alzheimer's Society report. In the original submission, these costs were not correctly transferred from the model cost calculation sheet to the model input sheet.
- The company included a simple PAS discount of [redacted] to all the economic model results.

Based on the above amendments the company new base-case results are as summarised in Table 5.3.

Table 5.3: Updated base-case results (list and PAS price)

Technology	Total			Incremental			ICER (list price)	ICER (PAS price)
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs		
Updated transition matrix								
SoC	[redacted]							
Lecanemab	[redacted]							
+ Updated Clarity AD patient count data								
SoC	[redacted]							
Lecanemab	[redacted]							
+ Correct health state costs								
SoC	[redacted]							
Lecanemab	[redacted]							
Updated base-case								
SoC	[redacted]							
Lecanemab	[redacted]							
Based on Company response to clarification letter, Table 53[10] AD = Alzheimer's disease; ICER = incremental cost-effectiveness ratio; LYG = life years gained; PAS = patient access scheme; QALY = quality-adjusted life-year; SoC = standard of care								

EAG comment: No comments.

5.2 Company's sensitivity analyses

The company performed and presented the results of probabilistic sensitivity analysis (PSA), one-way sensitivity analyses as well as scenario analyses.

A probabilistic sensitivity analysis (PSA) was run with 10,000 iterations, varying the uncertain parameters. The PSA excluded structural assumptions (e.g., cell links for model options, time horizon) and those considered to be certain (e.g., drug acquisition costs), to demonstrate the variance around the ICER.

The PSA resulted in a probabilistic ICER just [redacted] lower than the base-case ICER.

Table 5.4: PSA base-case results

Technology	Total		Incremental		
	Costs (£)	QALYs	Costs (£)	QALYs	ICER (per QALY)
SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lecanemab	[redacted]	[redacted]			

Based on CS Table 67[2]
CS = company submission; ICER = incremental cost effectiveness ratio; PSA = probabilistic sensitivity analysis; QALY = quality-adjusted life-year; SoC = standard of care

The company conducted a one-way sensitivity analysis (OWSA) by varying one parameter at a time and assessing the subsequent impact on cost effectiveness. Parameters were varied within their 5% and 95% CIs or +/- 20% in the absence of CI data. The following parameters were identified as most influential on the cost effectiveness of lecanemab versus SoC:

- Time to worsening HRs for mild AD
- Time to worsening for MCI due to AD
- The Farina patient-by-proxy health state utility values for mild, moderate, and severe AD.

According to the CS, the variation in results is likely driven by the Farina et al[1] study uncertainty as the SEs were very large compared to the means, rather than the health state utility values.

According to the CS, the scenario analyses showed that the ICER improves in most scenarios versus the base-case. Based on the Company's scenario analyses, modelling assumptions that have the greatest effect on the ICER were:

- Modelling caregiver utility as the absolute QoL for both caregivers and patients summed in each cycle.
- Setting baseline age to 60 years
- Switching to natural history data at baseline (0 years).

EAG comment: No comment.

5.3 Subgroup analysis

According to the company, no formal subgroup analysis was performed due to the lack of statistically significant differences in treatment effects among subgroups in the Clarity AD trial. Separate scenarios for MCI due to AD and mild AD populations were carried out in the company's scenario analysis and

found ICERs of [redacted] and [redacted] for MCI due to AD and mild AD respectively (company's original base-case, probabilistic).

EAG comment: In the final scope issued by NICE, *APoE4* gene carrier status, MCI due to AD and mild AD were listed under subgroups to be considered for subgroup analysis. The EAG requested that the subgroup analysis of *APoE4* be conducted. In their response to clarification question A9, the company carried out an *APoE4* non-carrier subgroup scenario. The *APoE4* non-carrier subgroup, *APoE4* homozygous subgroup and *APoE4* heterozygous subgroup analysis led to a [redacted], [redacted] and [redacted] compared with the corrected base-case list price ICER, respectively (Table 5.5

For these subgroup analyses, the company used subgroup-specific:

- Patient counts for the transition probabilities up to 18 months,
- HRs
- AE rates
- Compliance
- Exposure and discontinuation
- Mean patient weight, and
- Baseline health state membership (see Tables 17-21 of response to clarification questions)

Table 5.5: Summary of subgroup analysis based on the *APoE4* carrier status

Scenario	Incremental Costs	Incremental QALYs	ICER	ICER including PAS	% difference vs. base-case ICER (inc. PAS)
Updated company base-case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
APoE4 non-carrier subgroup	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
APoE4 homozygotes subgroup	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
APoE4 heterozygotes subgroup	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Based on Company response to clarification letter, Table 54 [10]
APoE4 = apolipoprotein E4; ICER = incremental cost effectiveness ratio; QALY = quality-adjusted life-year; PAS = patient access scheme

5.4 Model validation and face validity check

5.4.1 Face validity assessment

No face validity assessment of the health economic model (assumptions) was provided in CS section B.3.14.

5.4.2 Technical verification

The company reported that technical verification was performed once by the primary modeller and once by a modeller external to the project and that any issues were addressed. According to CS section B.3.14.1 the technical verification included:

- Cell-by-cell checks of formulae
- Rebuilding of key sections of the model
- Logical tests
- A full audit of model inputs.

5.4.3 Comparisons with other economic models

The company made a comparison with the SoC of the current model with the economic models included in the cross-comparison challenge for AD models as part of the IPECAD Modelling Workshop. Two comparisons were performed 1) with 100% of the population starting in MCI due to AD (CS Table 73) and; 2) with 100% of the population starting in mild AD (CS Table 74).

5.4.4 Comparison with external data used to develop the economic model

The distribution of the cohort across the MCI due to AD, mild, moderate and severe AD and death health states for the first 18 months estimated in the economic model were compared with Clarity AD (CS Tables 71-72 for the lecanemab and SoC arm, respectively).

5.4.5 Comparison with external data not used to develop the economic model

No comparison with external data (e.g., registry data) not used to develop the economic model was provided in CS section B.3.14.

EAG comment: The main concerns of the EAG relate to: a) inconsistency between estimated outcomes with the company model and observed data from Clarity AD; b) inconsistency between estimated outcomes with the company model and model in the published literature; c) internal validity checks performed by the company and; d) face validity assessment.

a) In CS Tables 71 and 72 a comparison with the CS model and Clarity AD was made with regards to health state occupancy over time. The company stated that "*The model accurately predicts the state occupancy observed in Clarity AD for both treatments. The minor differences, particularly in mortality, may be explained by the use of life tables in combination with AD mortality estimates from published literature*." According to the EAG this conclusion is debatable. The differences between the CS model and Clarity AD differ between the health states. For instance, for the "MCI due to AD" health state, the 18-month health state occupancy is almost identical for both treatments while the 18-month health state occupancy for the "Severe AD" health state is substantially overestimated. These differences are unlikely to be explained by the reasons highlighted in the CS (i.e., "*life tables in combination with AD mortality estimates from published literature*"). In response to clarification question B28, the company acknowledged "*that the health state occupancy for the 'Severe AD' state is over-estimated in both the lecanemab and SoC arms of the model compared with the observed occupancy in Clarity AD*". However, the company stated that "*the differences between lecanemab and SoC are relatively consistent between Clarity AD and the model*". The EAG agrees that the differences between lecanemab and SoC are more consistent with Clarity AD than the absolute health state occupancy at 18 months. However, these deviations are not considered "minor" by the EAG and from clarification response Table 76 it becomes clear that the economic model systematically overestimates the lecanemab benefits compared with Clarity AD in terms of health state occupancy in the moderate AD, severe AD and death health states. Moreover, the EAG notes that for the validity assessment comparing model outcomes with data used to develop the economic model, the absolute outcomes are equally important as the incremental outcomes. Based on the current assessment, the EAG considers that the

company's economic model does not accurately predict the state occupancy as observed in Clarity AD for both treatments and that there is a potential bias favouring the effectiveness of lecanemab. This might be related to the issue raised by the EAG in clarification question B10, i.e., potential technical errors in the estimation of transition probabilities to multiple health states and their conversion to a different period length matching the cycle length.

b) CS Tables 73 and 74 provide a comparison of duration of state occupancy (years) compared with the IPECAD modelling challenge models. The company stated that "*Overall, this economic analysis shows comparable results to other published models, particularly those with comparable settings*". According to the EAG this conclusion is debatable. In CS Table 73, it becomes apparent from the models that included the "severe AD" health state, that "mild AD" is commonly the health state with the second longest duration of occupancy, while only for the CS model the health state with the second longest duration of occupancy was the "severe AD" health state. More specifically, occupancy in the "severe AD" health state was 23% in the company's analysis while for the other models this ranged between 2%-11%. The company stated in response to clarification question B31 that the "*cause of differences in health state occupancy between models is not fully known. However, the rate of mortality is expected be a key determinant of time spent in the severe AD state. When using mortality data from Potashman et al.*" … "*the proportion and duration of time spent in each state is more consistent with published models*".[10] The EAG agrees that the change of rate of mortality improves the consistency with published models (clarification response Tables 80-83).

c) The Company's response to clarification question B29 provides more clarity on the internal validity checks performed by the company. This is reassuring to the EAG.

d) No explicit face validity assessment and comparison with external data not used to develop the economic model in B.3.14. However, the company provided information related to the advisory board meetings that considered the face validity of the model (assumptions).

6 EVIDENCE REVIEW GROUP'S ADDITIONAL ANALYSES

6.1 Exploratory and sensitivity analyses undertaken by the EAG

Table 6.1 summarises the key issues related to the cost effectiveness categorised according to the sources of uncertainty as defined by Grimm et al. 2020:[59]

- Transparency (e.g., lack of clarity in presentation, description, or justification)
- Methods (e.g., violation of best research practices, existing guidelines, or the reference case)
- Imprecision (e.g., particularly wide confidence intervals, small sample sizes, or immaturity of data)
- Bias and indirectness (e.g., there is a mismatch between the decision problem and evidence used to inform it in terms of population, intervention/comparator and/or outcomes considered)
- Unavailability (e.g., lack of data or insight).

Identifying the source of uncertainty can help determine what course of action can be taken (i.e., whether additional clarifications, evidence and/or analyses might help to resolve the key issue). Moreover, Table 6.1 lists suggested alternative approaches, expected effects on the cost effectiveness, whether it is reflected in the EAG base-case as well as additional evidence or analyses that might help to resolve the key issues.

Based on all considerations in the preceding Sections of this EAG report, the EAG defined a new base-case. This base-case included multiple adjustments to the original base-case presented in the previous sections. These adjustments made by the EAG form the EAG base-case and were subdivided into three categories (derived from Kaltenthaler 2016):[60]

- Fixing errors (FE) (correcting the model where the company's submitted model was unequivocally wrong)
- Fixing violations (FV) (correcting the model where the EAG considered that the NICE reference case, scope or best practice had not been adhered to)
- Matters of judgement (MJ) (amending the model where the EAG considers that reasonable alternative assumptions are preferred).

Table 6.1: Overview of key issues related to the cost effectiveness

Key issue	Section	Source of uncertainty	Alternative approaches	Expected impact on ICER[a]	Resolved in EAG base-case[b]	Required additional evidence or analyses
11. Starting distribution of patients between MCI due to AD and mild AD in the economic model not in line with UK clinical practice	4.2.6	Bias and indirectness	Change to UK practice	+	Explored	Yes
12. Possible methodological errors in estimation of and questionable validity of transition probabilities	4.2.6	Methods	Follow best practices / multistate model?	-	No	Yes
13. Extrapolation of long-term treatment effect might be implausible	4.2.6	Unavailability	Treatment effect waning / off-treatment use SoC transitions	+	Explored	Yes
14. Mortality estimates in MCI due to AD state in the economic model are implausible	4.2.6	Bias and indirectness	MCI mortality = general population	+	Yes	No
15. Uncertainty about treatment discontinuation in the economic model	4.2.6	Bias and indirectness, unavailability	Explore best approaches to treatment discontinuation	+	Explored	Yes
16. Methodological uncertainty about approach to estimating utility values lacks face validity	4.2.8	Methods	Mixed effects model	+/-	No	Yes
17. Uncertainty in caregiver disutility due to patient institutionalisation	4.2.8	Bias and indirectness	Disable caregiver disutility	+	Yes	No
18. No AE disutilities applied	4.2.8	Methods	Change AE durations, disutilities,	+/-	No	Yes

Key issue	Section	Source of uncertainty	Alternative approaches	Expected impact on ICER[a]	Resolved in EAG base-case[b]	Required additional evidence or analyses
			include grade ½ ARIA			
19. Cost and resource use discrepancies between the company's economic model and the NHS England Alzheimer's MCI model	4.2.9	Imprecision/ methods	Use NHSE model costs	+	Yes	No
20. Inclusion of health state costs outside the NHS and PSS perspective on costs	4.2.9	Methods	Exclude private care costs	+	No	Yes
21. Inconsistency between estimated outcomes with the company model and observed data from Clarity AD	5.3	Bias and indirectness	Repeat validation after re-estimating transition probabilities	+/-	No	Yes

[a] Likely conservative assumptions (of the intervention versus all comparators) are indicated by '-'; while '+/-' indicates that the bias introduced by the issue is unclear to the EAG and '+' indicates that the EAG believes this issue likely induces bias in favour of the intervention versus at least one comparator; [b] Explored
AD = Alzheimer's disease; AE = adverse event; ARIA = amyloid-related imaging abnormality; EAG = Evidence Assessment Group; ICER = incremental cost-effectiveness ratio; MCI = mild cognitive impairment; NHS = National Health Service; NHSE = NHS England; PSS = Personal Social Services; SoC = standard of care; UK = United Kingdom

6.1.1 EAG base-case

Adjustments made by the EAG, to derive the EAG base-case (using the CS base-case as starting point) are listed below. Table 6.2 shows how individual adjustments impact the results plus the combined effect of all above-mentioned adjustments simultaneously, resulting in the EAG base-case.

1. MJ: Patient baseline distribution MCI/mild AD changed to 38%/62%
2. FV: Use SoC transition probabilities in (community and institution) mild AD /MCI due to AD health states
3. MJ: Disable severity-based stopping rule
4. MJ: Set mortality equal to that of general population in MCI due to AD health state
5. MJ: Use treatment-independent utility values
6. MJ: Disable caregiver institutionalisation disutility
7. MJ: Use NHS cost model estimates
8. FV: Use diagnostic costs for all tested.

6.1.2 EAG exploratory scenario analyses

The EAG performed the following exploratory scenario analyses to explore the impact of alternative assumptions conditional on the EAG base-case.

6.1.2.1 Exploratory scenario analyses

1. Disable all-cause treatment (tx) discontinuation after trial period
2. Disable all-cause tx discontinuation after trial period but enable severity-based stopping rule
3. Disable institutionalisation-based stopping rule scenario
4. Disable backward transitions
5. Use pessimistic imputation (missing = moderate AD) for transition probability analysis
6. Use multistate survival analysis transition probabilities
7. Mortality estimates informed by Potashman et al[33]
8. Cap utility values at general population values
9. Assume two thirds of direct non-medical costs are private costs.

6.1.3 EAG subgroup analyses

The EAG performed scenarios setting the model to 100% of people starting in the MCI due to AD/mild AD health states respectively. The EAG also performed subgroup analyses for *APoE4* non-carriers, *APoE4* homozygotes and *APoE4* heterozygotes.

6.2 Impact on the ICER of additional clinical and economic analyses undertaken by the EAG

In Section 6.1 the EAG base-case was presented, which was based on various changes compared to the company base-case. Table 6.2 shows how individual changes impact the results plus the combined effect of all changes simultaneously. The exploratory scenario analyses are presented in Table 6.3. These are all conditional on the EAG base-case. The analyses numbers in Tables 6.2 and 6.3 correspond to the numbers reported in Section 6.1. Finally, Table 6.4 provides the results of the subgroup analysis (described in Section 6.1.3). The submitted model file contains technical details on the analyses performed by the EAG (e.g., the "EAG" sheet provides an overview of the cells that were altered for each adjustment). All results are deterministic as the programming of the PSA resulted in not all EAG changes to be propagated in the PSA.

Table 6.2: EAG base-case

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
CS base-case					
Lecanemab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SoC	[redacted]	[redacted]			
1. Patient baseline distribution MCI/mild AD changed to 38%/62%					
Lecanemab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SoC	[redacted]	[redacted]			
2. Off-treatment (community and institution) mild/MCI states should have SoC TPs					
Lecanemab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SoC	[redacted]	[redacted]			
3. Disable severity-based stopping rule					
Lecanemab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SoC	[redacted]	[redacted]			
4. Mortality in MCI set HR=1					
Lecanemab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SoC	[redacted]	[redacted]			
5. Use treatment-independent utility values					
Lecanemab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SoC	[redacted]	[redacted]			
6. Disable caregiver institutionalisation disutility					
Lecanemab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SoC	[redacted]	[redacted]			
7. NHS cost model changes					
Lecanemab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SoC	[redacted]	[redacted]			
8. Diagnostic costs for all tested					
Lecanemab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SoC	[redacted]	[redacted]			
EAG base-case					
Lecanemab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SoC	[redacted]	[redacted]			

Results deterministic unless indicated.

AD – Alzheimer's disease; CS = company submission; EAG = Evidence Assessment Group; HR= hazard ratio; ICER = incremental cost-effectiveness ratio; MCI = mild cognitive impairment; NHS = National Health Service; QALY = quality-adjusted life year; SoC = standard of care; TPs = transition probabilities

Table 6.3: Deterministic scenario analyses (conditional on EAG base-case)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
EAG base-case					
Lecanemab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SoC	[redacted]	[redacted]			
1. Disable all-cause tx discontinuation after trial period					
Lecanemab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SoC	[redacted]	[redacted]			

2. Disable all-cause tx discontinuation after trial period but enable severity-based stopping rule					
Lecanemab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SoC	[redacted]	[redacted]			
3. Disable institutionalisation-based stopping rule scenario					
Lecanemab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SoC	[redacted]	[redacted]			
4. Backward transitions disabled					
Lecanemab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SoC	[redacted]	[redacted]			
5. Use pessimistic imputation (assume missing = moderate) for transition probability analysis					
Lecanemab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SoC	[redacted]	[redacted]			
6. Multistate survival analysis transition probabilities					
Lecanemab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SoC	[redacted]	[redacted]			
7. Mortality estimates informed by Potashman et al[33]					
Lecanemab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SoC	[redacted]	[redacted]			
8. Cap utility values at general population values					
Lecanemab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SoC	[redacted]	[redacted]			
9. Assume 2/3 of direct non-medical are private costs					
Lecanemab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SoC	[redacted]	[redacted]			

Results deterministic unless indicated.
EAG = Evidence Assessment Group; ICER = incremental cost-effectiveness ratio; QALYs = quality-adjusted life years; SoC = standard of care; tx = treatment

Table 6.4: Deterministic subgroup analyses (conditional on EAG base-case)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
EAG base-case					
Lecanemab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SoC	[redacted]	[redacted]			
MCI due to AD					
Lecanemab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SoC	[redacted]	[redacted]			
Mild AD					
Lecanemab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SoC	[redacted]	[redacted]			
***APoE4* non-carriers**					
Lecanemab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SoC	[redacted]	[redacted]			
***APoE4* homozygotes**					
Lecanemab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SoC	[redacted]	[redacted]			

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
***APoE4* heterozygotes**					
Lecanemab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SoC	[redacted]	[redacted]			
Results deterministic unless indicated. AD = Alzheimer's disease; *ApoE4* = apolipoprotein E4; EAG = Evidence Assessment Group; ICER = incremental cost-effectiveness ratio; MCI = mild cognitive impairment; QALYs = quality-adjusted life years; SoC = standard of care					

6.3 EAG's preferred assumptions

The estimated EAG base-case ICER based on the EAG preferred assumptions highlighted in Section 6.1, was £[redacted] per QALY gained. The most influential adjustments were: using SoC transition probabilities for patients that discontinued treatment in MCI due to AD and mild AD, the cost changes made based on the NHS England cost model and disabling the severity-based stopping rule. The ICER increased most in the scenario analysis where backward transitions were disabled, utility values were capped at general population values, and all-cause treatment discontinuation was disabled after the trial period.

6.4 Conclusions of the cost effectiveness section

The company presented a health economic model in line with the NICE reference case, with the exception that some of the included costs may have been outside the NHS and PSS perspective (private costs included in direct non-medical costs). Uncertainties related to the decision problem include the generalisability of concomitant treatments and SoC to UK clinical practice. The impact of this is unknown. Some important model parameters were not based on SLRs but hand searches, but the EAG is reassured that overall, the best possible sources of evidence were identified and that the impact of this uncertainty is low. [redacted]

The most important uncertainties were observed in treatment effectiveness and related to the following key issues:

The health state occupation of the modelled starting population was likely not in line with UK clinical practice (key issue 11). The estimation of transition probabilities likely induced errors due to multiple transitions in the trial period and this is reflected in discrepancies between health state occupation in trial versus model, especially for the moderate and severe AD states (key issues 12 and 21). This should be addressed and in that light the company's alternative multistate survival model might be of interest, although it should be explored in how far this addressed the issue of competing risks. As highlighted by the company, the lack of long-term relative effectiveness evidence means there is uncertainty about the treatment effect of lecanemab, and this is not sufficiently explored in the CS (key issue 13). The EAG recommends that the impact of treatment effect waning be explored. In addition, the company's assumption that patients that discontinue treatment with lecanemab in the MCI due to AD and mild AD states continue to have the treatment effectiveness of lecanemab for as long as they are residing in these states is likely inappropriate – and the EAG's change of this assumption had the highest impact on the ICER. Mortality estimates for the MCI due to AD group are lower than those of the general population but this is likely induced by some limitations in the analysis where these were derived from (key issue 14) and the EAG prefers to assume that mortality in this state is no worse than in the general population. Treatment discontinuation is likely over-estimated in the company's model due to double-

counting (key issue 15): all-cause treatment discontinuation is modelled as a constant rate beyond the trial follow-up period, and severity- and institutionalisation-based stopping rules are in place as well. The company have not yet confirmed a severity-based stopping rule and a hard stopping rule does not seem to be in line with the draft SmPC[6]. The EAG therefore recommends that the severity-based stopping rule be disabled, and that it should be considered how treatment discontinuation is best included in the model.

Related to the estimation of HRQoL, the EAG is concerned that the company's analysis does not consider within/between-patient variability, ignores potential confounding variables and potentially oversimplifies results through not capturing changes to utility over time (key issue 16). The EAG proposes that a mixed effects model be explored for the analysis of the utility values. In the meantime, the EAG prefers the use of treatment-independent utility values. It should also be noted that utility values for the MCI due to AD and mild AD health states are higher than the UK age and gender matched general population utilities. There is limited evidence on the impact of institutionalisation on the HRQoL of caregivers and the EAG preferred disabling the utility decrement associated with institutionalisation (key issue 17). The impact of AEs on HRQoL is likely not appropriately captured and should be further explored in terms of AE duration, disutilities and inclusion of grade 1 and 2 ARIA events (key issue 18).

For resource use and costs, the EAG noted discrepancies in some resource use and cost estimates between the company's model and the NHS England model and implemented the estimates from the NHS England model (key issue 19). The EAG also noted that some health state costs were likely outside the NHS and PSS perspective on costs, as they were likely private care costs (key issue 20).

In conclusion, there is significant uncertainty about various aspects in this appraisal and it may be possible to address some of this with further data collection, collection of expert opinion, and further analyses. Further data collection may help inform: long-term effectiveness of lecanemab (with the caveat that unanchored indirect treatment comparisons are prone to bias) and rates of institutionalisation in this population. Collection of expert opinion may inform the health state occupation in the starting population and appropriateness of stopping rules. Further analyses may help address the methodological uncertainty in the estimation of transition probabilities in the presence of competing risks and utilities, as well as assess the impact of inclusion of adverse events (with the duration also informed by experts).

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Maastricht University

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

Addendum with cost scenarios

Produced by Kleijnen Systematic Reviews Ltd. in collaboration with Erasmus University Rotterdam (EUR) and Maastricht University

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None.

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Commercial in confidence (CiC) data are highlighted in blue throughout the report.

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

Marie Westwood acted as project lead and systematic reviewer on this assessment, critiqued the clinical effectiveness methods and evidence and contributed to the writing of the report. Sabine Grimm and Bram Ramaekers acted as health economic project leads, critiqued the company's economic evaluation and contributed to the writing of the report. Willem Witlox, Bradley Sugden, Teebah Abu-Zahra, Xiaoyu Tian and Nigel Armstrong acted as health economists on this assessment, critiqued the company's economic evaluation and contributed to the writing of the report. Kevin McDermott acted as a systematic reviewer, critiqued the clinical effectiveness methods and evidence and contributed to the writing of the report. Caro Noake critiqued the search methods in the submission and contributed to the writing of the report. Manuela Joore acted as health economist on this assessment, critiqued the company's economic evaluation, contributed to the writing of the report and provided general guidance.

Table 1: Additional scenarios on costs estimated in the NHS England model

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
CS base-case					
Lecanemab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Standard of Care	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lecanemab administration costs £565 instead of £207.59					
Lecanemab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Standard of Care	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MRI frequency increased					
Lecanemab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Standard of Care	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CSF and test scan cost increased					
Lecanemab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Standard of Care	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

1. Exploratory scenario analysis including APOE4 test costs

Exploratory scenario analyses were performed to explore the impact of including APOE4 test costs and related costs in the lecanemab arm of the model.

A one-off cost of £444 was applied to the lecanemab arm of the model. This consisted of the following cost and resource use items:

- £250 for the price of the test applied to 80% of the modelled population that was assumed to take up genetic testing (in line with NHS England model as per email communication).
- One outpatient follow-up appointment costed at £200 for all patients that underwent genetic testing (in line with NHS England model as per email communication).
- Genetic counselling at a cost of £350, assumed to be taken up by 30% of those that underwent genetic testing (in line with the NHS England model as per email communication).

Table 1.1: Exploratory scenarios on inclusion of APOE4 test costs (PAS price)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Company base-case with APOE4 test costs					
Lecanemab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Standard of Care	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG base-case with APOE4 test costs					
Lecanemab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Standard of Care	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MCI due to AD with APOE4 test costs					
Lecanemab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Standard of Care	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mild AD with APOE4 test costs					
Lecanemab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Standard of Care	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
APOE4 non-carriers with APOE4 test costs					
Lecanemab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Standard of Care	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
APOE4 homozygotes with APOE4 test costs					
Lecanemab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Standard of Care	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
APOE4 heterozygotes with APOE4 test costs					
Lecanemab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Standard of Care	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years. Results deterministic unless indicated.

EAG response to company addendum April 2024

General comments

The EAG's ability to scrutinize the company's changes was hampered by the fact that the company did not signpost where the changes were made in the model – and that the company did not provide the changes in results per individual change. But most importantly, the company's updated model contains major structural changes that were not detailed in the addendum and that may affect the results. One of these changes includes [redacted]. This leads to major changes in the model engine that could not be verified in the short time span available, and without further documentation. All company results thus must be interpreted with caution.

Company change 1: Test costs

The EAG notes that the company's failure rate adopted here is based on the screening failure rate for Aβ positivity in Clarity AD (where 28.80% of patients failed the Tier 5 screening for Aβ pathology), while the EAG's analysis is based on the DSU report which assumed a 43.08% failure rate.

Therefore, this issue is not resolved, and the appropriate failure rate should be discussed.

The difference in costs of testing for the population is £429.65 in the company's update vs £537.44 using the EAG analysis which is based on the failure rate suggested in the DSU report.

Company change 2: Mortality in MCI due to AD

The company's change to the mortality hazard ratio (i.e. assuming equal mortality in the MCI due to AD health state compared to the general population) is in line with the EAG analysis and has been checked in the model – this issue is resolved, with the caveat of the issue raised in the general comments (i.e. major structural changes make it difficult to assess the impact). For an assessment of the impact of this change, we refer to the original EAG analysis.

Company change 3: Method for utility estimation

The company adopted a mixed model for repeated measures (MMRM) with a backward elimination approach (ITT FAS+ dataset) including the following candidate independent variables as fixed effects:

- baseline EQ-5D utility index score
- treatment group
- use of AD symptomatic medication at baseline
- APOE4 carrier status
- geographical region
- health state defined by CDR-SB at the time of observation
- presence of treatment-emergent infusion-related reactions, ARIA-E, or ARIA-H (any grade) at the time of observation.

This was done separately for patient-reported EQ-5D, patient-by-proxy EQ-5D and caregiver EQ-5D.

Patient-reported EQ-5D

The final model considering self-reported EQ-5D utilities ([redacted]), included the following covariates: baseline EQ-5D utility index score, treatment group, geographical region and health state defined by CDR-SB at the time of observation. Results suggested treatment with lecanemab was associated with an increase in EQ-5D utility score ([redacted]). Notably, the mild AD health state was associated with a higher EQ-5D index score ([redacted] [moderate AD as reference], p=[redacted]) than MCI due to AD ([redacted] [moderate AD as reference], p=[redacted]).

Patient-by-proxy EQ-5D

The final model considering self-reported EQ-5D utilities ([redacted]), included the following covariates: baseline EQ-5D utility index score, treatment group, APOE4 carrier status, geographical region and health state defined by CDR-SB at the time of observation. Results suggested treatment with lecanemab was associated with an increase in EQ-5D utility score ([redacted]). Unlike the patient self-reported results, less severe health states were associated with higher EQ-5D utility scores, as would be expected, with the coefficients decreasing with increasing AD severity (MCI due to AD: [redacted]; mild AD: [redacted] [moderate AD as reference], all [redacted]).

Caregiver EQ-5D

The final model considering self-reported EQ-5D utilities ([redacted]), included the following covariates: baseline EQ-5D utility index score, APOE4 carrier status, geographical region and health state defined by CDR-SB at the time of observation. Results suggested that less severe health states defined by patient CDR-SB were also associated with higher EQ-5D utility scores for caregivers, with the coefficients decreasing across AD severity levels (MCI due to AD: [redacted], p=[redacted]; mild AD: [redacted], p=[redacted] [moderate AD as reference]).

EAG comment:

General

The methods used by the company are considered reasonable in general and an improvement compared with the original CS approach. However, the diagnostics of the MMRM were not provided and thus could not be assessed by the EAG, mainly:

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

Further, it is unclear how the utility values in Table 15 of the company's addendum are exactly calculated (e.g. whether the Geographical region – Europe covariate is included in the calculation).

Patient-reported EQ-5D and patient-by-proxy EQ-5D

The company included a fixed effects covariate for treatment group, resulting in an [redacted] utility for patients treated with lecanemab. However, this covariate is not significant (when considered the commonly used α=0.05) and should thus potentially be removed from the model to be in line with the backward elimination approach.

In addition to the above, it is unclear whether the updated utilities (Table 15 of the company's addendum) can be considered to have face validity given that the utility values for the MCI due to AD and mild AD health states are [redacted] than the UK age and gender matched general population utilities.The company stated that although the NICE reference case is to use patient-reported utilities, patient-by-proxy utilities were preferred in the base case due to the counterintuitive results observed for the patient-reported MMRM based on one clinician's feedback in the UK HTA advisory board.

In line with expert opinion, the EAG would prefer to use the patient-reported EQ-5D for MCI due to AD and mild AD (in line with the NICE reference case and expert opinion) but acknowledges the counter-intuitive results. The EAG recommends removing the fixed effects covariate for treatment group (in line with the backward elimination approach and the commonly used α=0.05).

In summary, the company's new approach is an improvement, but questions remain about the appropriateness of using proxy utility values for all health states, the face validity of the utility values and the appropriateness of treatment-independent utility values.

Company change 4: Adverse events

The company partly addressed key issue 18 by exploring longer AE duration for grade 3+ ARIA events. However, the company did not address the EAG's concerns that AE disutilities may be under-estimated, and did not incorporate AE disutilities for grade 1 and 2 ARIA AEs . This issue is thus partly resolved.

Company change 5: Number of MRI scans

This issue is partly resolved. The EAG has verified the company's change to the number of MRI scans modelled in the first year. The EAG had also amended the number of MRI scans in the following year, based on the NHS England model and the EAG's clinical expert – the company have not amended this. This issue is thus partly resolved.

Company scenario 1: Treatment duration

The company provided a scenario in which the costs for lecanemab [redacted] The EAG considers that this would be an extreme scenario in terms of cost-saving, while it is not accompanied by the same extreme assumptions in the [redacted] The EAG was unable to reproduce this scenario, or validate its implementation, given the time constraints.

Company scenario 2: NHS England costs

The company consider their own costing more appropriate than the costs reported in the NHS England model. The EAG agrees that not all costs in the NHS England model are clearly referenced. Ideally, further clarification would be provided by NHS England on the costs used.

Company scenario 3: APOE4 testing

The company's scenario differs with respect to the proportion taking up APOE4testing: the EAG scenario included [redacted] of people taking up APOE4 testing according to communication with the NHS England team.

Company scenario 4: Utility cap

The company's scenario capping utility at the general population values appears appropriate and in line with EAG suggestions, although this could not be verified in the model.

Single Technology Appraisal

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

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 1 March 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 EAG preferred base case and scenarios

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
On page 29 (Table 1.23): ICER for "[redacted] mild/MCI states should have SoC tps": £[redacted]	The company propose the ICER for "[redacted] mild/MCI states should have SoC tps" scenario on page 29 is corrected to: £[redacted]	The ICER reported by the EAG is inaccurate for the scenario described. The company have matched this ICER by setting W6:X6 and AA6:AB6 in the 'Engine_Lec' sheet to 0%, which results in SoC transition probabilities for <u>all</u> patients who have discontinued in MCI and mild AD health states, including those who stop treatment due to all-cause discontinuation. The corrected ICER reported by the company is obtained by setting only cells AA6:AB6 to 0%, therefore only applying SoC transition probabilities to patients who discontinue treatment due to [redacted] in the MCI and mild AD health states, as described in the EAGs scenario.	This scenario was indeed meant to disable the treatment effect in patients off treatment, in community and institution health states. The EAG justification for this change can be found in EAG comment 4.2.6 c) in the EAG report: "The EAG changes this in the base-case, instead assuming no treatment effect in patients off-treatment in MCI and mild AD health states and is interested in further justification for this modelling choice." To make it clearer that it is both for community and institution settings, the wording has been changed to "Off-

			treatment (community and institution) mild/MCI states should have SoC TPs".
On page 118: "The EAG explored a scenario analysis excluding backward transitions, which increases the ICER substantially, from the company base-case ICER (with PAS) £[redacted] to £[redacted]."	The company propose the wording on page 118 is edited to read: "The EAG explored a scenario analysis excluding backward transitions, which increases the ICER, from the company base-case ICER (with PAS) £[redacted] to £[redacted]."	This is a misrepresentation. The ICER increases by [redacted]%, which does not constitute a substantial increase. As the ICERs will be redacted, it is imperative that ICERs are described accurately. Additionally, this scenario does not accurately reflect the lecanemab treatment effect observed in Clarity AD, as a greater percentage of patients moved from mild AD to MCI due to AD in the lecanemab arm than in the placebo arm.	Not a factual inaccuracy.
On page 112: "In the company's scenario analysis using the transitions to death based on Potashman et al. in which the risk of death was constant, the ICER substantially increased by	The company propose the wording on page 112 is edited to read: "In the company's scenario analysis using the transitions to death based on Potashman et al. in which the risk of death was constant, the ICER	This is a misrepresentation. The ICER increases by [redacted]%, which does not constitute a substantial increase. As the ICERs will be redacted, it is imperative that ICERs are described accurately.	Not a factual inaccuracy.

[redacted]% compared with the corrected base-case PAS ICER."	increased by [redacted]% compared with the corrected base-case PAS ICER."		

Issue 2 Population and Aβ testing

Description of problem	Description of proposed amendment	Justification for amendment	EAG
On page 15 (Table 1.2): "The population in the key clinical trial, Clarity AD, and of those eligible for lecanemab is narrower than that specified in the NICE final scope (although the economic analysis section of the scope does state "the use of lecanemab is conditional on the presence of amyloid pathology"), being defined by the presence of Aβ pathology", On page 35: "The actual population in the key clinical trial, Clarity AD, and of those eligible for lecanemab is narrower",	The company propose the wording on page 15 and page 100 is edited to read: "The population in the key clinical trial, Clarity AD, and of those eligible for lecanemab, is in line with the NICE final scope". The company propose the wording on page 35 is removed.	Whilst the population specified in the NICE final scope is "People with mild cognitive impairment or mild dementia due to Alzheimer's disease", it is specified in the economic analysis section of the final scope that "The use of lecanemab is conditional on the presence of amyloid pathology", as acknowledged by the EAG on page 100. As such, the early AD population with confirmed Aβ pathology in Clarity AD is not narrower than the final scope.	Not a factual inaccuracy – the NICE scope population section does not specify the presence of amyloid pathology, as reflected in Table 1 of the CS, notwithstanding the requirement to include the cost of diagnostic testing specified in the economic analysis section.

And on page 100: "The population in the key clinical trial, Clarity AD, and of those eligible for lecanemab was narrower than that specified in the NICE final scope, in that the inclusion criteria for Clarity AD required confirmation of the presence of amyloid beta (Aβ) pathology using either a CSF amyloid protein test or amyloid PET scan".			
On page 15 (Table 1.2): "This testing is not routinely used to diagnose AD. Therefore, a recommendation to use lecanemab will imply several consequences on cost and potentially health: • the cost of the testing • any harm to those tested, which includes more than those who	The company propose the wording on page 15 is edited to read: "This testing is not routinely used to diagnose AD. Therefore, a recommendation to use lecanemab will imply several consequences on cost" The company propose the wording on pages 35 and 100 is edited to read: "As stated in the CS, this testing is not routinely used in the National Health Service (NHS) to diagnose AD. Therefore, there are consequences of this testing that need to be valued to assess the effectiveness and cost	As per section 5.9 of the NICE reference case, "If a diagnostic test to establish the presence or absence of this biomarker is carried out solely to support the treatment decision for the specific technology, the associated costs of the diagnostic test should be incorporated into the assessments of clinical and cost effectiveness". Therefore, the approach in the CS and clarification	Not a factual inaccuracy.

would be eligible for lecanemab” And on pages 35 and 100: “As stated in the CS, this testing is not routinely used in the National Health Service (NHS) to diagnose AD. Therefore, there are consequences of this testing that need to be valued to assess the effectiveness and cost effectiveness of lecanemab. These include the cost of testing and any potential harms to health of those tested, who include more patients than those who turn out to be eligible for lecanemab.”	effectiveness of lecanemab. This includes the cost of testing for those tested, who include more patients than those who turn out to be eligible for lecanemab”.	question responses is aligned with the NICE reference case.	
On page 15 (Table 1.2): “ICER will increase”.	The company propose the wording on page 15 is edited to read: “ICER will marginally increase”.	To align with the EAG’s description of the expected impact on the ICER for other key issues, for which the magnitude of change is specified. As per the company’s response to clarification question B20 a), the scenario in which	Not a factual inaccuracy – it is unknown what the effect of including any harm of the diagnostic test on those tested might be.

		diagnostic testing costs for all tested are included, the ICER increases by [redacted]%. As the ICERs will be redacted, consistency and accuracy in the description of the impact on the ICER are imperative.	
On page 112: "The CSR Table 14.1.4.1.1 reports on the ITT FAS+, however the weight reported in CS Table 37 is inconsistent with CSR Table 14.1.4.1.1 (69.8 versus 71.1; see Table 4.6 above). Moreover, the baseline proportions reported for MCI due to AD and mild AD are in CSR Table 14.2.3.8.1 (and used in the CS base-case) are inconsistent with those reported for the ITT FAS+, ITT Food and Drug Administration (FDA) FAS and SAS in CSR Tables 14.1.4.1.1-14.1.4.1.3. The EAG presumes that this difference can be explained	The company propose the wording on page 112 is edited to read: "The CSR Table 14.1.4.1.1 reports on the ITT FAS+, however the weight reported in CS Table 37 is inconsistent with CSR Table 14.1.4.1.1 (69.8 versus 71.1; see Table 4.6 above). Moreover, the baseline proportions reported for MCI due to AD and mild AD are in CSR Table 14.2.3.8.1 (and used in the CS base-case) are inconsistent with those reported for the ITT FAS+, ITT Food and Drug Administration (FDA) FAS and SAS in CSR Tables 14.1.4.1.1-14.1.4.1.3. This discrepancy is explained by the company on page 138 of the CS: "*To reflect the UK population as closely as possible, the weight distribution of the European ITT population (n=390) of Clarity AD was used for the weight distribution. The*	The EAG are correct that the CSR tables referenced in the CS are incorrect. However, on page 138 of the CS, the company explain how these values are informed: "To reflect the UK population as closely as possible, the weight distribution of the European ITT population (n=390) of Clarity AD was used for the weight distribution. The associated mean weight was 69.76 kg ([redacted])". As such, speculation that the difference in values can be explained by the definition of MCI due to AD and mild AD is incorrect.	Not a factual inaccuracy. The speculation was regarding the difference in the baseline proportions reported for MCI due to AD and mild AD. For weight it is factually stated that CS Table 37 and CSR Table 14.1.4.1.1 are inconsistent.

by the definition of MCI due to AD and mild AD, either through CDR-SB (CS base-case; CS Table 37) or case report form (CS Table 10), both based on the ITT FAS+."	*associated mean weight was 69.76 kg ([redacted])".*"		

Issue 3 SoC comparator in MCI and mild AD

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
On page 16 (Table 1.3): "AChEis and memantine are not licensed for use in this population."	The company propose the wording on page 16 is edited to read: "AChEis and memantine are not licensed for use in the MCI due to AD population."	While the table heading indicates that the text is referring to the MCI due to AD population, this is not clear from the text within the table and it is important to differentiate MCI due to AD from mild AD given licensed treatments differ for these populations.	Not a factual inaccuracy, however, the within table wording has been amended for clarity.
On page 16 (Table 1.3): "When patients who received symptomatic AD medication (AChEi or memantine) were excluded,	The company propose the wording on page 16 is edited to read: "When patients who received symptomatic AD medication (AChEi or memantine) were excluded, the	Clarity AD was not powered to detect differences versus placebo in this group of patients, which represents a subgroup of a subgroup.	Not a factual inaccuracy.

the adjusted mean difference in change from baseline, for lecanemab vs. placebo, at 18 months, for CDR-SB in the MCI subgroup, was reduced from [redacted], representing a [redacted]% reduction in decline to [redacted] (95% CI: [redacted] to [redacted]), representing a [redacted]% reduction in decline."	adjusted mean difference in change from baseline, for lecanemab vs. placebo, at 18 months, for CDR-SB in the MCI subgroup, was reduced from [redacted], representing a [redacted]% reduction in decline to [redacted] (95% CI: [redacted] to [redacted], N=[redacted] [lecanemab: n=[redacted], placebo: n=[redacted]), representing a [redacted]% reduction in decline. These results should be interpreted with caution as Clarity AD was not powered to detect differences versus placebo in this subgroup."		
On pages 21 and 76: "the EAG considers that the results of the subgroup analyses raise a question about whether lecanemab has a clinically significant effect, in patients with MCI due to AD, when used in the context of UK SoC (i.e., without concomitant symptomatic AD treatment)." On page 101:	The company propose the wording on pages 21, 76 and 101 is edited to acknowledge that conclusions cannot be drawn from the results of the subgroup analyses as to the significance of effect of lecanemab in patients with MCI due to AD without concomitant symptomatic AD treatment, as Clarity AD was not powered to detect differences versus placebo in this subgroup.	Clarity AD was not powered to detect differences versus placebo in this group of patients, which represents a subgroup of a subgroup.	Not a factual inaccuracy.

“In addition, the EAG considers that the results of the subgroup analyses for the MCI due to AD population, excluding those receiving concomitant treatment with AChEi or memantine, raise a question about whether lecanemab has a clinically significant effect, in patients with MCI due to AD, when used in the context of UK SoC (i.e., without concomitant symptomatic AD treatment);”			
On page 16 (Table 1.3): “The ICER would probably increase because the treatment effect goes down for all outcome measures.”	The company propose that the following sentence is added beneath this sentence in the same section of the table: “However, the ICER marginally decreases when AChEi and memantine costs are excluded from health states in which they are off-label (clarification question B22 d).”	As acknowledged by the EAG in Section 4.2.9.6 and provided by the company in response to clarification question B22 d), including symptomatic treatments from health states in which they are off-label leads to a minor decrease in the ICER. This should be acknowledged alongside the impact on the	Not a factual inaccuracy – the scenario that the company refer to in response to clarification question B22d only adjusted costs and not treatment effect.

		ICER of treatment effect within the same subgroup.	
On page 17 (Table 1.4): "Potential undertreatment of the comparator group, for this population, could lead to overestimation of the effects of lecanemab. However, it should be noted that the percentage of patients in the mild subgroup of the Clarity AD trial who received AChEi was not that much less than 70%."	The company propose the wording on page 17 is edited to read: "The impact on estimation of the effect of lecanemab is unknown. It should be noted that the percentage of patients in the mild subgroup of the Clarity AD trial who received AChEi was not that much less than 70%."	This is inaccurate as the proportions of patients receiving AChEis and memantine were comparable across treatment arms in Clarity AD, therefore it is inaccurate to state that this could overestimate the effects of lecanemab. As per the company's response to clarification question A16, of patients with MCI due to AD, in the lecanemab arm [redacted]% of patients received an AChEi and [redacted]% received memantine; in the placebo arm, [redacted]% received an AChEi and [redacted]% received memantine. Of patients with mild AD, in the lecanemab arm [redacted]% of patients received an AChEi and [redacted]% received memantine; in the placebo arm, [redacted]% received an AChEi	Not a factual inaccuracy.

		and [redacted]% received memantine.	
On page 17 (Table 1.4): "Unclear, but the difference will probably not be large if the clinical expert's estimate of AChEi use is correct" with regard to the expected effect on cost-effectiveness estimates.	The company propose the wording on page 17 is edited to read: "The ICER is expected to decrease, but the difference will probably not be large if the clinical expert's estimate of AChEi use is correct."	For other key issues, the EAG speculate as to the direction of change on the ICER. For consistency, the text should state that the ICER would be expected to decrease given the increased reduction in decline from baseline for CDR-SB for lecanemab versus placebo at 18 months.	Not a factual inaccuracy.
On page 37: "The company amended the comparator for mild dementia to including no AChEi in the decision problem." And on page 112: "As described in Section 2.2, the company amended the comparator for mild AD to including no AChEi."	The company propose the wording on page 37 is updated to read: "The company amended the comparator for mild dementia due to AD to an AChEi and/or non-pharmacological management." The company propose the wording on page 112 is updated to read: "As described in Section 2.2, the company amended the comparator for mild AD to an AChEi and/or non-pharmacological management."	The wording "including no AChEI" is unclear and should be replaced with the exact wording used by the company in the CS B.1.1.	Not a factual inaccuracy. However, to improve clarity, the wording has been amended to: 'The company amended the comparator for mild dementia to *"AChEi and/or non-pharmacological management,"* i.e. including the possibility of no AChEi in the decision problem.'

On page 55: "The EAG questions whether the proportions of participants in Clarity AD who were receiving concomitant symptomatic AD medications are likely to be consistent with current UK clinical practice." And on page 101: "For the population with mild dementia due to AD, the proportion of Clarity AD study participants receiving AChEi (approximately [redacted]) was not substantially [redacted] than the 70%, estimated by clinical expert opinion to be typical in the UK. In addition, whilst the proportion of study participants in this group receiving memantine (approximately [redacted]) was substantially [redacted] than the 5%, estimated by clinical expert opinion."	The company propose the wording on page 55 is updated to read: "The EAG questions whether the proportions of participants in Clarity AD who were receiving concomitant symptomatic AD medications are likely to be consistent with current UK clinical practice. There is uncertainty surrounding this, highlighted by differing estimates obtained through clinical opinion sought by the EAG versus that sought by the company." The company propose the wording on page 101 is updated to read: "For the population with mild dementia due to AD, the proportion of Clarity AD study participants receiving AChEi (approximately [redacted]) was not substantially [redacted] than the 70%, estimated by clinical expert opinion to be typical in the UK. In addition, whilst the proportion of study participants in this group receiving memantine (approximately [redacted]) was substantially [redacted] than the 5%, estimated by clinical expert opinion, clinical opinion sought by the company suggests 10% of patients with mild AD would be	These sentences are misrepresentative as the clinical feedback sought by the company at the clarification stage is not mentioned, implying that the feedback sought by the EAG is the only input available.	A summary of the responses of clinical experts (n=3), from the source document (data on file) provided at the clarification stage, has been added to the text on page 55.

And on page 112-113: "Moreover, it was stated that AChEis and memantine will be administered to approximately 70% and 5% of people with mild AD respectively."	treated with memantine, suggesting uncertainty regarding the proportions seen in UK clinical practice." The company propose the wording on page 112-113 is updated to read: "Moreover, it was stated by the clinician sought by the EAG that AChEis and memantine will be administered to approximately 70% and 5% of people with mild AD respectively. However, clinical opinion sought by the company suggests 10% of patients with mild AD would be treated with memantine, suggesting uncertainty regarding memantine use in clinical practice."		

Issue 4 Clinical subgroups

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
On page 22: "Unclear" with regard to expected effect on the cost effectiveness estimates.	The company propose the wording on page 22 is edited to read: "ICER will likely decrease in non-carriers and increase in carriers".	To align with the expected impact on the cost effectiveness estimates provided by the EAG for key issue 4. The company	Amended.

		previously provided exploratory scenario analyses in response to clarification questions; these analyses included subgroup-specific time to worsening HRs, patient counts, AEs, compliance, discontinuation, mean patient weight, and baseline health state distribution. Although these scenarios were exploratory only for the purposes of responding to clarification questions, the ICER decreased for non-carriers and increased in carriers.	
On page 78: "Subgroup analyses, by ApoE4 genotype, showed a consistent pattern of reduced or absent lecanemab treatment effect across the four cognitive and functional outcome measures"	The company propose the wording on page 78 is edited to read: "Subgroup analyses by ApoE4 genotype showed a marginally increased treatment effect compared with placebo on CDR-SB and ADCOMS, a comparable treatment effect compared with placebo on ADCS-MCI-ADL and ADAS-Cog-14 in ApoE4 heterozygotes, and a reduction in treatment effect compared with placebo in ApoE4 homozygotes across the four	It is inaccurate that a consistent pattern of reduced or absent treatment effect across cognitive and functional outcomes was seen across all ApoE4 carriers, as is implied in the current wording.	Amended.

	cognitive and functional outcome measures”		
On page 101: “This is particularly notable for the homozygous ApoE4 carrier population, where the adjusted mean difference in change from baseline in CDR-SB was 0.28 (22% faster decline, confidence interval including no effect).” The sentence refers to Figure 3.14, the forest plot of subgroup analysis for adjusted mean difference in CDR-SB.	The company propose the wording on page 101 is edited to read: “This is particularly notable for the homozygous ApoE4 carrier population, where the adjusted mean difference in change from baseline in CDR-SB was 0.28 (22% faster decline, confidence interval including in favour of lecanemab).”	The statement that the confidence internal “includes no effect” infers that the confidence interval does not cross zero, which is incorrect.	Not a factual inaccuracy – a CI that crosses zero implies the inclusion of no effect.
On page 141: “For these subgroup analyses, the company used subgroup-specific patient counts for the transition probabilities up to 18 months, subgroup-specific HRs and AE rates”	The company propose the wording on page 141 is edited to read: “For these subgroup analyses, the company used subgroup-specific: • Patient counts for the transition probabilities up to 18 months, • HRs • AE rates	The list provided by the EAG is not exhaustive and therefore inaccurate, as it infers that subgroup-specific compliance, exposure and discontinuation, mean patient weight, and baseline health state membership were not	This has been amended

	• Compliance • Exposure and discontinuation • Mean patient weight, and • Baseline health state membership”	utilised by the company in the subgroup analyses.	

Issue 5 Treatment effect

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
On pages 19-20 (Table 1.7): “The absolute difference of 0.45 on CDR-SB is about the same as achieved by existing anticholinesterase drugs for AD (that are symptomatic rather than influencing rate of decline) and most people now believe their benefit is clinically meaningful. This is despite the size of effect being less than the cited minimum	The company propose this statement is removed from the quote from the clinician.	The statement implies that the effect on CDR-SB achieved through treatment with AChEIs is equivalent to that achieved through treatment with lecanemab, which is inaccurate. The statement “The absolute difference of 0.45 on CDR-SB is about the same as achieved by existing anticholinesterase drugs for AD” is misleading, as the reference to a 0.45 change in CDR-SB refers to the adjusted mean treatment	Not a factual inaccuracy – The text is a quote, which forms part of a discussion of the magnitude of effect that is likely to be considered clinically meaningful.

clinically important difference of >1.”		difference for lecanemab compared to the placebo arm at 18 months. As shown in Table 3.7, the proportions of patients receiving concomitant symptomatic AD medications (which include AChEis) were comparable across treatment arms in Clarity AD. Therefore, the difference of 0.45 on CDR-SB would be due to lecanemab treatment effect on top of any concomitant AChEi usage.	
On pages 19-20 (Table 1.7): “This is problematic and likely to be different at different disease stages. Importantly, Individual patients/families will have very different views on what is meaningful for them, depending on their differing values and expectations. When deciding whether to prescribe lecanemab, I would be strongly influenced by their views in each	The company propose the following wording is added to page 20 (Table 1.7), following the wording described: “This 20-30% benefit in oncology stated by the clinician aligns with published estimates of MCID for CDR-SB, as per stated in the CS Section B.2.12.1: “A 20-30% reduction in decline compared to placebo in CDR-SB is as an appropriate benchmark for clinical meaningfulness.[1–4]”	The inclusion of the opinion of the EAG’s clinical expert and the exclusion of the published MCID values for CDR-SB, as referenced in the CS Section B.2.12.1, infer that the clinical opinion sought by the EAG is the only available information on MCID in CDR-SB, thereby ignoring four peer-reviewed publications presented in the CS.	The following text has been added to Table 1.7, pg 20: ‘Studies cited in the CS, in support of the clinical significance of the treatment effect indicate that an increase of between 1 and 2 points on CDR-SB would be considered a clinically significant decline; the reported adjusted mean

individual case. I think somewhere between 20 and 40% would apply for most people and so sounds about right to me, but this benefit would have to outweigh treatment burden and risks. In oncology, a 20-30% benefit in the right direction seems to be considered clinically meaningful without any question.”			between group difference in change from baseline was -0.451 over 18 months.’
On page 66: “The apparent beneficial effects of lecanemab were not consistent across all components of ADAS-Cog 14, however, the direction of effect was generally in favour of lecanemab (Figure 3.5).” On page 69: “The apparent beneficial effects of lecanemab were not consistent across all components of ADCS-ADL-MCI-14, however, the direction of effect was	The company propose the wording on page 66 is edited to read: “The apparent beneficial effects of lecanemab were not consistent across all components of ADAS-Cog 14, however, the direction of effect was in favour of lecanemab for all components except constructional praxis (Figure 3.5).” The company propose the wording on page 69 is edited to read: “The apparent beneficial effects of lecanemab were not consistent across all components of ADCS-MCI-ADL, however, the direction of effect was	The direction of effect for ADAS-Cog 14 and ADCS-ADL-MCI is in favour of lecanemab for all components excluding one component of ADAS-Cog-14, with statistical significance achieved for 11 of the 18 components of ADCS-MCI-ADL. As the figures will be redacted, accurate descriptions are vital. Additionally, ADCS-MCI-ADL is incorrectly referred to on page 69 as “ADCS-ADL-MCI-14”.	Not a factual inaccuracy

generally in favour of lecanemab (Figure 3.9).”	consistently in favour of lecanemab for all components.”		
On page 137: “The most important uncertainties were observed in treatment effectiveness and related to the health state occupation of the modelled starting population (potential bias); the estimation of transition probabilities (methodological uncertainty); mortality (potential bias); institutionalisation (unavailability); and lack of long-term relative effectiveness estimates (unavailability). Most of these uncertainties have a potentially high impact on cost effectiveness.”	The company propose the wording on page 137 is edited to read: “The most important uncertainties were observed in treatment effectiveness and related to the health state occupation of the modelled starting population (potential bias); the estimation of transition probabilities (methodological uncertainty); mortality (potential bias); institutionalisation (unavailability); and lack of long-term relative effectiveness estimates (unavailability). The impact of these uncertainties has an unknown impact on cost effectiveness.”	The statement regarding ICER impact is inaccurate. The modelled starting population does not have a high impact on ICER, as evidenced by the scenario in which the baseline starting population is changed from MCI:mild 78.8%:21.2% to 38%:62% (increase of [redacted]%). The impact of an alternative source of institutionalisation and of the lack of long-term data on the ICER is unknown.	Amended the last sentence to read: “For some of these uncertainties, the impact on cost effectiveness could be high.”

Issue 6 Generalisability of Clarity AD to the UK

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
On page 21: "The EAG considers that the concomitant use of symptomatic AD medication (AChEis and memantine) in the Clarity AD study was unlikely to reflect UK clinical practice, particularly with respect to the management of patients with MCI due to AD."	The company propose the wording on page 21 is edited to read: "The EAG considers that the concomitant use of symptomatic AD medication (AChEis and memantine) in the MCI due to AD population in the Clarity AD study was unlikely to reflect UK clinical practice. The use of concomitant AChEIs in the mild AD group is [redacted] than the proportion suggested by clinical expert opinion sought by the EAG (70%, compared with [redacted]% in the lecanemab and [redacted]% in the placebo arm)."	In Section 2.3 of the EAG report, the EAG acknowledge that the proportion of mild AD patients receiving an AChEI in Clarity AD is similar to the clinical expert's estimation of 70%. This is not reflected in Table 1.8, which implies concomitant drug usage for all subgroups and all treatments is misaligned. The text should be updated to reflect the wording from Section 2.3.	The text in Table 1.8, pg 21 has been amended to: 'The EAG considers that (with the exception of the use of AChEis in the mild AD subgroup), the concomitant use of symptomatic AD medication (AChEis and memantine) in the Clarity AD study was unlikely to reflect UK clinical practice; the apparent discrepancy is most notable with respect to the management of patients with MCI due to AD.'
On page 23: "The proportions of patients who have MCI due to AD or mild AD used in the model are not in line with what is likely seen in UK clinical	The company propose the wording on page 23 is edited to read: "The proportions of patients who have MCI due to AD or mild AD used in the model may not be in line with what is likely seen in UK clinical practice"	This statement is based on the opinion of one clinician. The text does not acknowledge the clinical validation sought by the company through an advisory board, from which the consensus was that Clarity	Not a factual inaccuracy, see further related issues below.

practice” regarding description of the key issue.		AD was reflective of UK clinical practice. Additionally, the text does not acknowledge the clinical expert opinion sought by the company in response to clarification question B7, in which another clinician agreed that the proportions of MCI versus mild AD in Clarity AD are likely to be reflective of UK clinical practice: Page 72, clarification response document: “Another clinician stated that the proportions of mild AD versus MCI due to AD will change a lot over time with the spread of brain health clinics and access to blood-based biomarkers, so the proportions seen in Clarity AD are likely to reflect what will be seen in UK clinical practice.”	
On page 23: “Formal elicitation of expert opinion” regarding	The company propose the wording on page 23 is edited to read:	The statement does not acknowledge the UK HTA advisory board previously	Not a factual inaccuracy.

additional evidence or analyses that might help to resolve this key issue.	"Further formal elicitation of expert opinion".	conducted by the company and implies that formal expert opinion has not previously been elicited.	
On page 111: "In Clarity AD, 62% had MCI and 38% had mild dementia (see Table 4.6 above). In the UK, patients are currently more likely to present at the mild dementia than MCI stage, and so the proportions offered lecanemab might be reversed (i.e., 38% MCI, 62% mild dementia) according to clinical opinion obtained by the EAG. This is supported by the company's response to clarification question B7."	The company propose the wording on page 111 is edited to remove the statement: "This is supported by the company's response to clarification question B7."	This is inaccurate. The company sought clinical expert opinion in response to clarification question B7 on page 72 of the clarification response document: "They would expect the initial population to be weighted more towards mild AD as those patients are more reliably followed up. Over time the proportion of MCI due to AD patients is expected to increase" and "the proportions of mild AD versus MCI due to AD will change a lot over time with the spread of brain health clinics and access to blood-based biomarkers, so the proportions seen in Clarity AD are likely to reflect what	Not a factual inaccuracy. The response to clarification question supports that the (initial) population is more weighted towards mild AD. Changes over time, in the future, regarding the population UK clinical practice are not considered in this section of the EAG report.

		will be seen in UK clinical practice." It is not accurate that this response supports the clinical opinion obtained by the EAG. The clinician who provided the latter response agreed that the proportions seen in Clarity AD are likely to reflect what will be seen in UK clinical practice, opposing the opinion of the EAG's clinical expert. The clinician who provided the first response qualified their statement with a time component, which is not captured in the current wording.	
On page 150: "The health state occupation of the modelled starting population was likely not in line with UK clinical practice"	The company propose the wording on page 150 is edited to read: "The health state occupation of the modelled starting population was likely not in line with current UK clinical practice"	The statement does not acknowledge that current clinical practice is unlikely to be reflective of future clinical practice following the introduction of a DMT for early AD. This is supported by the clinical opinion sought by the company in response to clarification question B7 on	Not a factual inaccuracy, this is based on expert opinion obtained by the EAG.

		page 72 of the clarification response document: "Over time the proportion of MCI due to AD patients is expected to increase" and "the proportions of mild AD versus MCI due to AD will change a lot over time with the spread of brain health clinics and access to blood-based biomarkers".	
Throughout the report, it is implied that the company used 62% and 38% as the base case for the baseline MCI due to AD and mild AD proportions, respectively, when the EAG mentions reversing these proportions in their preferred base case. However, the company base case used was 78.8% and 21.2% for MCI due to AD and mild AD, respectively.	Text on these pages should be amended to make clear that the 38%/62% preferred base case used by the EAG is not a reversal of the company's base case, which was 78.8%/21.2%.	Factual inaccuracy. The 62%/38% split of baseline MCI due to AD and mild AD is based on clinical definitions as per the Clarity AD protocol and outlined in Table 10 of the CS. The 78.8%/21.2% split is based on CDR-SB scores and uses the pooled baseline health state distribution from both lecanemab and SoC patients.	Not a factual inaccuracy. It is not stated that 62%/38% are used in the CS base-case. Indeed, EAG Tables 4.6 and 4.7 clearly highlight the proportions used in the CS base-case

This occurs on: Page 111-112 Page 118			

Issue 7 MRI monitoring

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
On page 22: "There is also some uncertainty around what ARIA-related criteria are recommended to trigger suspension of dosing and what criteria were applied in the Clarity AD study."	The company propose the wording on page 22 is removed.	Treatment recommendations including suspensions and discontinuation of dosing for ARIA-E and ARIA-H across severities and symptoms were presented in the CS Section B.2.3.1.2, Figure 10. Therefore, it is inaccurate to state that there is "uncertainty" around this in the context of Clarity AD.	The following detail (already included in section 3.2.2 of the EAG report) has been added to Table 1.10, pg 22: 'There appears to be some inconsistency between the reported treatment suspension criteria used in Clarity AD and [redacted]

			[redacted]
On page 22: "It is unclear whether safety monitoring requirements should vary by ApoE4 genotype"	The company propose the wording on page 22 is edited to read: "[redacted] in the draft SmPC."	In the draft SmPC for lecanemab, [redacted] It is therefore inaccurate to state this is unclear.	Not a factual inaccuracy – The text on page 22 is questioning whether monitoring requirements should vary, given the evidence of differential risk by ApoE4 genotype.
On page 22: "Provision of more detail about safety monitoring undertaken during the Clarity AD study (Clarification question A23)." regarding alternative approaches	The company propose the wording on page 22 is edited to read: "Provision of more detail about safety monitoring undertaken during the Clarity AD study (completed in response to clarification questions A22 and A23)."	Additional specific details from Clarity AD regarding [redacted] were provided in response to clarification question A23. This question is mentioned by the EAG in their statement, however it is not acknowledged that this information was provided by the company. Additionally, details on MRI safety monitoring were provided in response to clarification question A22, which is not mentioned by the EAG.	Amended.

suggested by the EAG.			
On page 22: “Provision of data on adverse events of special interest (primarily ARIA) by ApoE4 genotype subgroup.” regarding alternative approaches suggested by the EAG and additional evidence or analyses might help to resolve this key issue.	The company propose the wording on page 22 is edited to read: “Provision of data on adverse events of special interest (primarily ARIA) by ApoE4 genotype subgroup (provided in response to clarification question A9).”	The statement implies these data are yet to be provided, however, the company provided these data in response to clarification question A9.	Amended.

Issue 8 Transition probabilities

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
On page 24: "Best practices not followed for estimation of transition probabilities under competing risks"	The company propose the wording on page 22 is edited to remove the statement.	This statement does not reflect the company's attempt to follow the tutorial by Gidwani et al., suggested by the EAG, nor the reasons that this was not possible. As per the company response to clarification question B10, page 94 of the clarification response document: "Option 1 would not be possible, as this would require severely limiting structural assumptions, for example restricting patients movement so that patients can only remain in their current health state, or progress to the next most severe health state in any given cycle, which would not be consistent with the natural history data"	Not a factual inaccuracy

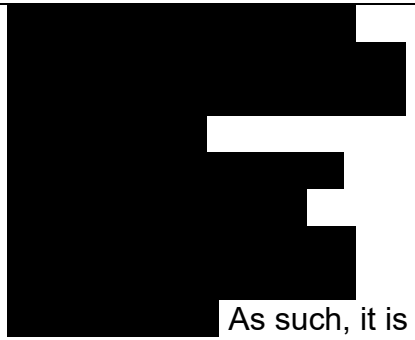
		“Option 3 is only feasible with three possible transitions.” “The eigen decomposition of the transition matrix was estimated [option 3], however this resulted in negative transition probabilities for some transitions, as forewarned by Gidwani et al.”	
On page 29: “i.e., potential technical errors in the estimation of transition probabilities to multiple health states and their conversion to a different period length matching the cycle length. Hence, this error should be corrected”	The company propose the wording on page 29 is edited to read: “i.e., potential technical errors in the estimation of transition probabilities to multiple health states and their conversion to a different period length matching the cycle length.”	This statement “this error should be corrected” implies that an error was identified by the EAG. It was acknowledged by the EAG in the clarification call that no specific error was identified in the calculation of the transition probabilities, as detailed in the company response to clarification question B10, page 94 of the clarification response document: “The wording of the question implies an error had been identified in the CS model, however it was acknowledged	Not a factual inaccuracy – what is meant here is the resulting error from not accounting for competing risks.

		by the EAG during the clarification TC on 10th January 2024 that no specific errors had been identified." As such, this statement should be removed.	
On page 115: "Of these three studies, only one, Potashman et al, was deemed an appropriate source for transition probabilities across the disease stages".	The company propose the wording on page 115 is edited to read: "Of these three studies, only one, Potashman et al, reported transition probabilities across all disease stages".	The wording is inaccurate.	Not a factual inaccuracy.
On page 122: "However, patients who did not complete the core study due to early discontinuation from AEs, withdrawal of consent, or loss to follow-up did not attend the study visit at month 18 were excluded from the calculation of transition probabilities".	The company propose the wording on page 122 is edited to read: "However, patients who did not attend the study visit at month 18 were excluded from the calculation of transition probabilities".	The company acknowledge this wording is as per the CS page 119 and would like to flag a correction. Not all patients who discontinued due to reasons listed did not attend the 18-month visit.	Amended.

Issue 9 Long-term treatment effect

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
On page 24: "Long-term treatment effect based on assumptions: the hazard ratio estimated from the trial holds throughout model time horizon for patients on treatment (and those discontinued in MCI due to AD and mild AD states)."	The company propose the wording on page 24 is edited to read: "Long-term treatment effect based on assumptions: the hazard ratio estimated from the trial holds throughout the model time horizon"	The treatment effect HRs were estimated under the ITT principle and therefore implicitly reflect the impact of discontinuation, therefore it would be inaccurate to not apply this in MCI due to AD and mild AD health states.	Not a factual inaccuracy
On page 24: "Provide justification for approach of assuming lecanemab transition for patients off-treatment in MCI due to AD and mild AD states." regarding additional evidence or analyses that might help to resolve the key issue.	The company propose the wording on page 24 is removed.	Rationale for this approach was provided by the company in the CS pages 124 and 153.	This has been amended to read: "Provide further information regarding how the numbers of patients in the modelled off-treatment MCI due to AD and mild AD states compare to those in the observed off-treatment MCI due to AD and mild AD states in Clarity AD. Provide further explanation on the appropriateness of

			assuming no reduction in the lecanemab treatment effect on treatment and in the lecanemab arm off-treatment MCI due to AD and mild AD health states in the long term, given that: • the treatment effect was estimated based on all patients in the trial, most of whom were on treatment (only 17.9% discontinued), so it cannot be applicable to patients off-treatment • patients discontinue at potentially different rates beyond the end of study follow-up • even on treatment, the treatment effect might reduce with time”
On page 122:	The company propose the wording on page 122 is edited to read:	As detailed in the CS page 125, [redacted]	This has been amended.

“In addition, the EAG is concerned that the model also includes this treatment effect beyond the 18 months observed trial period. This means that the model currently assumes a long-term treatment effect for patients that are off-treatment in the model.”	“In addition, the EAG is concerned that the model also includes this treatment effect beyond the 18 months observed trial period. This means that the model currently assumes a long-term treatment effect for patients that are off-treatment in the MCI due to AD and mild AD health states.”	 As such, it is inaccurate to state that “the model currently assumes a long-term treatment effect for patients that are off-treatment in the model”.	

Issue 10 Health-related quality of life

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
On page 26: “When applying utilities in the model, utility decrements were additively applied, deviating from best practice recommendations in NICE DSU TSD 12.”	The company propose the wording on page 26 is edited to read: “When applying utilities in the model, utility decrements were additively applied.” The company propose the wording on page 128 is removed.	NICE DSU TSD 12 recommends the multiplicative approach when combining utilities for two comorbid conditions, that is, when an individual has both condition A and condition B. All health states included in the	Different interpretation of the NICE DSU TSD 12 and therefore not a factual inaccuracy.

On page 128: "Use of a multiplicative approach, using adjusted baselines, is currently recommended by NICE (NICE Decision Support Unit (DSU) TSD 12)"		economic model are mutually exclusive; that is, an individual cannot be in both health state A and health state B. Therefore, the TSD recommendation for the multiplicative approach does not hold for health state utility values in the model.	
On page 26: "The scenario capping utility values increased the ICER substantially."	The company propose the wording on page 26 is edited to read: "The scenario capping utility values increased the ICER".	The scenario in question was presented by the company in response to clarification question B17 b). The ICER increases by [redacted]% versus the base case ICER, which the company do not believe constitutes a substantial increase. The EAG do not describe the magnitude of increase for other key issues, other than for the APOE4 homozygote subgroup, for which "substantial" is used to describe an increase of [redacted]%. As the ICERs will be redacted, consistency and accuracy in the description of the impact on the ICER are imperative.	Amended.

On page 126: "Clarity AD measured patient HRQoL using EQ-5D-5L, Quality of life in Alzheimer's disease (QOL-AD), and Zarit's Burden Interview (ZBI) at baseline and every six months. The patient's study partner also served as the patient's proxy, completing the EQ-5D-5L and QOL-AD on the patient's behalf, in addition to for themselves."	The company propose the wording on page 26 is edited to read: "Clarity AD measured patient self-reported HRQoL using EQ-5D-5L and Quality of life in Alzheimer's disease (QOL-AD) at baseline and every six months. The patient's study partner also served as the patient's proxy, completing the EQ-5D-5L and QOL-AD on the patient's behalf. In addition, study partners completed a self-assessment of EQ-5D-5L and Zarit's Burden Interview (ZBI)."	The company acknowledge that it was incorrectly stated on page 129 of the CS that ZBI was used to measure patients HRQoL, which is a measure of burden among caregivers of adults with dementia and was completed by study partners only. It is incorrect that study partners completed the QOL-AD for themselves. As detailed on page 129 of the CS, the patient's study partner served as the patient's proxy and completed the EQ-5D-5L and QOL-AD on the patient's behalf, in addition to their own EQ-5D-5L.	Amended.
On page 126: "Following advice from one clinician in a UK HTA advisory board, patient-reported utilities were utilised for MCI due to AD and mild AD health states, whilst proxy-reported estimates	The company propose the wording on page 126 is edited to read: "Following advice from clinicians in a UK HTA advisory board, in which one clinician stated it would be appropriate to switch to caregiver proxy reported utility values at moderate or severe AD, and another	In response to clarification question B19, the company clarified an error in the reference to the July 2023 UK HTA advisory board in the CS. The correct interpretation is used by the EAG on page 130: "In the company's HTA advisory board meeting, one	The EAG recognises that the highlighted text should also have been adjusted following clarification response. This text has now been replaced with the following: "In a UK HTA advisory board, one

were utilised for moderate and severe AD health states. However, another clinician recommended only switching to proxy-reported outcomes in the severe AD health state."	clinician stated that proxy values should be used for all stages of dementia, patient-reported utilities were utilised for MCI due to AD and mild AD health states, whilst proxy-reported estimates were utilised for moderate and severe AD health states."	clinician stated that it would be appropriate to switch to caregiver proxy reported utility values at moderate or severe AD, with another clinician stating that proxy values should be used for all stages of dementia. Other clinicians did not specify when would be best to switch". This is not currently reflected in the text on page 126 and should be amended.	clinician stated it would be appropriate to switch from patient-reported utilities to caregiver proxy utilities at moderate or severe AD health states, whilst another clinician stated that proxy values should be used for all stages of dementia. Following this, the company utilised patient-reported utilities for MCI due to AD and mild AD health states, with proxy-reported estimates being utilised for moderate and severe AD health states."
On page 127: "Disutilities applied were as follows: MCI due to AD: 0.00; Mild AD: 0.02; Moderate AD: 0.03; Severe AD: 0.02."	The company propose the wording on page 127 is edited to read: "Disutilities applied relative to the previous health state were as follows: MCI due to AD: 0.00; Mild AD: 0.02; Moderate AD: 0.03; Severe AD: 0.02."	As detailed on page 135 of the CS, these disutilities are relative to the previous health state, but this is not clear in the text.	Amended.
On page 130: "The company's selection to switch at the moderate AD health state was justified	The company propose the wording on page 130 is edited to read: "The company's selection to switch at the moderate AD health state, rather	As detailed in response to clarification question B19 a) in the clarification response document, this rationale was provided with regard to one	Not a factual inaccuracy. The response to CQ B19 a) is reflected in the preceding text that

through wanting to utilise patient-reported values so as not to deviate from the NICE reference case"	than utilise proxy-reported utilities for all health states, as suggested by one clinician, was justified through wanting to utilise patient-reported values so as not to deviate from the NICE reference case"	clinician's suggestion to utilise proxy-reported utility values for all health states. As such, the rationale was not explicitly used to inform the decision to switch at moderate AD.	reads: "In the company's HTA advisory board meeting, one clinician stated that it would be appropriate to switch to caregiver proxy reported utility values at moderate or severe AD, with another clinician stating that proxy values should be used for all stages of dementia."
On page 130: "The company provided results to the requested scenario analysis, utilising patient-reported utility values for all health states apart from the severe AD health state, which utilised proxy values. However, the company informed utilities for the moderate AD health state from Farina et al (mean [standard deviation, SD]: 0.8 [0.2])."	The company propose the wording on page 130 is edited to read: "The company provided results to the requested scenario analysis, utilising patient-reported utility values for all health states apart from the severe AD health state, which utilised proxy values. As there were insufficient observations in Clarity AD to reliably inform health state utilities for moderate AD (N=[redacted] for lecanemab, N=[redacted] for placebo), the company informed utilities for the moderate AD health state from Farina et al (mean [standard deviation, SD]: 0.8 [0.2])."	The statement by the EAG is a misrepresentation as it does not acknowledge the rationale for this decision, which was provided in response to clarification question B19 a).	Amended.

Issue 11 Cost and resource use

Description of problem	Description of proposed amendment	Justification for amendment	EAG respomse
On page 27: "Cost and resource use disparities were identified between the company's economic model and the NHS England Alzheimer's MCI model, including differences in unit costs, MRI safety monitoring, Aβ and ApoE4 testing, GP visits, quarterly outpatient reviews, and referral to local services". On page 109 (Table 4.5): Regarding the table row 'Evidence on resource use and costs', the EAG comment on company's submission states "Partly, some unit prices are not in line with the NHS England Alzheimer's MCI model"	The company propose the wording on page 27 is removed. The company propose the wording on page 109 regarding the table row 'Evidence on resource use and costs' is edited to read: "Consistent"	The wording on page 27 implies that the company has chosen not to comply with the NHS England Alzheimer's MCI model, however this was not available to the company until receiving the EAG report. In addition, the sources used in the NHS England Alzheimer's MCI model are unclear, with the majority of costs not being referenced, and others referencing input obtained via email from individual clinicians, rather than consensus from a group of clinicians, and failing to utilise to NHS reference costs where available, such as the cost of a lumbar puncture (HRG code HC72A). The unit costs and references used in the NHS England Alzheimer's MCI model compared with the	Not a factual inaccuracy.

		CS base case model are presented in Appendix A. The NHS England Alzheimer's MCI model therefore may not reflect the NICE reference case.	
On page 131: "…costs in the study by Paquete et al were informed by the Alzheimer's Society report and a US study by Robinson et al. These studies were used in the economic model to inform health state costs, direct medical and non-medical costs, and unpaid care costs."	The company propose the wording on page 131 is edited to read: "…costs in the study by Paquete et al were informed by the Alzheimer's Society report and a US study by Robinson et al. The Alzheimer's Society report and a ratio of costs between health states from Robinson et al were used in the economic model to inform health state costs, direct medical and non-medical costs, and unpaid care costs."	It is incorrect that Paquete et al. was used in the economic model. In addition, costs from Robinson et al. were not directly used in the model, but the ratio between health state costs from this study applied to costs from the Alzheimer's Society report to derive costs for MCI due to AD. The current wording implies that costs from a US study were used in the economic model.	Amended as suggested by the company.
On page 131: "…the administration cost for lecanemab was assumed to be the average cost of a simple parenteral chemotherapy infusion as reported in the NHS	The company propose the wording on page 131 is edited to read: "…the administration cost for lecanemab was assumed to be the average cost of a simple parenteral chemotherapy infusion as reported in the NHS reference costs 2021/22 (£207.59 per infusion), based on	As per page 139 of the CS. For other model inputs, the EAG provide the company's rationale for their choice, therefore this should be included for consistency.	Not a factual inaccuracy.

reference costs 2021/22 (£207.59 per infusion).”	clinical expert opinion during the UK HTA advisory board.”		
On page 135: “…the company assumed the screening failure rate for Aβ positivity of 28.80% from Clarity AD”	The company propose the wording on page 135 is edited to read: “…the screening failure rate for Aβ positivity of 28.80% was taken from Clarity AD”	Wording should be amended to clarify that the screening failure rate was taken from Clarity AD and was therefore not an assumption.	Amended by replacing “assumed” with “used”.
On page 135 (Table 4.18): Entire table	The company proposes that two columns are added to the table detailing the references for both the company’s and NHSEs unit costs, provided in Appendix A.	The sources used in the NHS England Alzheimer’s MCI model are unclear, with the majority of costs not being referenced, and others referencing input obtained via email with individual clinicians/NHSE employees, rather than consensus from a group of clinicians, or not utilising NHS reference costs where available. References should be provided to enable comparison with costs in the CS, which are referenced using sources aligning with the NICE reference case.	Not a factual inaccuracy.

Issue 12 Health state costs

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
On page 136: "The company acknowledged that it is therefore possible that the costs are not fully in line with the NICE reference case, but highlighted that it was not possible to estimate the proportion of costs from the Alzheimer's Society report that fall outside of the NICE reference case."	The company propose the wording on page 136 is edited to read: "The company acknowledged that it is therefore possible that the costs are not fully in line with the NICE reference case, but highlighted that it was not possible to estimate the proportion of costs from the Alzheimer's Society report that fall outside of the NICE reference case, nor was an alternative appropriate source of costs available."	As stated in the CS, Document B, Section B.3.5, and reiterated in response to clarification question B24 c), a suitable alternative to the Alzheimer's Society report to inform health state costs was not identified through the SLR nor through additional hand searches.	Not a factual inaccuracy.

Issue 13 Comparison of economic model outcomes with Clarity AD

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
On page 28: "From clarification response Table 76 it becomes clear that the economic model systematically overestimates	The company propose the wording on page 28 is edited to read: "From clarification response Table 76 it becomes clear that the economic model systematically overestimates	This is a misrepresentation of the data presented in Table 76 of the clarification response. The term "lecanemab benefits" is vague.	Not a factual inaccuracy. The statement is based on the "Difference" and "Difference in

the lecanemab benefits compared with Clarity AD in terms of health state occupancy in the moderate AD, severe AD and death health states."	health state occupancy for lecanemab and SoC compared with Clarity AD in the severe AD and death health states."		difference" rows of the cited Table. The term "lecanemab benefits" is explained in the same sentence "in terms of health state occupancy in the moderate AD, severe AD and death health states".
On page 28: "…there is a potential bias favouring the effectiveness of lecanemab."	The company propose the wording on page 28 is removed.	For the reasons described above, overestimation of health state occupation in the CEM vs. Clarity AD applies to both lecanemab and SoC, therefore it is inaccurate to state that the difference biases in favour of lecanemab.	Not a factual inaccuracy.
On page 142: "The 18-month health state occupancy for the "Severe AD" health state is substantially overestimated."	The company propose the wording on page 142 is edited to read: "The 18-month health state occupancy for the "Severe AD" health state is overestimated ([redacted]% for lecanemab, [redacted]% for SoC)."	The statement by the EAG is not quantified. Additionally, the company do not deem a [redacted]% overestimation to be substantial. The values will be redacted, therefore it is imperative that any description is accurate.	Not a factual inaccuracy. See Section 5.4 EAG comment for further details.

Issue 14 Treatment discontinuation

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
On page 25 (Table 1.16): “[redacted] And on page 123: [redacted] And on page 123: “[redacted].”	The company propose the wording on page 25 is edited to read: “[redacted] The company propose the sentences on page 123 are removed.	All-cause discontinuation in Clarity AD included reasons such as adverse events, withdrawal of consent, and patients’ choice, as presented in Section B.2.3.4 Table 11 in the CS. Stopping rules were only applied in the model, and not in the Clarity AD trial.	This is about the model and not a factual inaccuracy.
On page 113: “This was based on clinical expert opinion due to the absence of data from Clarity	The company propose the text on page 113 is edited to read:	This is a misrepresentation. There was no pre-defined stopping rule in Clarity AD, but there was consensus among clinicians in the UK HTA	Not a factual inaccuracy.

AD. However, based on CS Table 11, 22% patients did discontinue treatment, most patients discontinued due to adverse events (8%) or due to withdrawal of consent (8%), and none discontinued treatment due to inadequate therapeutic effect. Hence this does not support the stopping rule assumed by the company.”	“This was based on clinical expert opinion due to the absence of data from Clarity AD.”	advisory board conducted by the company that patients [redacted]. As per the issue highlighted in the row above, it would not be expected that all-cause discontinuation would align with a clinically defined stopping rule.	
On page 25 (Table 1.16): “[redacted] And on page 123: “[redacted]	The company propose the wording on page 25 is edited to read: “[redacted] The company propose the wording on page 123 is edited to read: “[redacted]	This is a misrepresentation as it implies that clinical expert opinion opposed [redacted]. There was consensus among clinicians in the UK HTA advisory board conducted by the company that [redacted]. Additionally, as per the company’s response to clarification question B12 a), Alzheimer’s Research UK stated that it is reasonable to assume [redacted]	Not a factual inaccuracy.

		[redacted]	
On page 123: “[redacted]	The company propose that the wording on page 123 is edited to read: “Mixed feedback was received from the company’s UK HTA advisory board on [redacted]	This is a misrepresentation as it does not reference that this was stated by one clinical expert in the UK HTA advisory board conducted by the company. [redacted]	This has been amended to read: “The company note that a time-based stopping rule would likely not be reflective of anticipated UK clinical practice, as the company’s UK HTA advisory board gave mixed feedback, including

			strong opposition due to varied response to treatment.”

Issue 15 Adverse events

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
On page 86: “The EAG notes that the incidence TEAEs leading to the interruption or withdrawal of the study drug was substantially higher in the lecanemab group than in the placebo group.”	The company propose that the wording on page 86 is edited to read: “The EAG notes that the incidence of TEAEs leading to the interruption of the study drug was higher in the lecanemab group than in the placebo group.”	This is a misrepresentation. The difference between lecanemab and placebo in the incidence of TEAEs leading to study drug withdrawal is [redacted]%. This does not constitute ‘substantially higher’.	Not a factual inaccuracy – The text refers to ‘TEAEs leading to <u>interruption or withdrawal</u> of the study drug’, NOT to withdrawal alone as implied in the company’s justification for amendment.
On page 125: “The prevalence of mild and moderate TEAEs (n(%)) was significantly higher in the lecanemab arm (mild:	The company propose the wording on page 125 is edited to read: “The prevalence of mild and moderate TEAEs (n[%]) was	The word “significantly” should be removed to avoid confusion with statistical significance.	Amended.

[redacted]; moderate: [redacted]) than the placebo arm (mild: [redacted]; moderate: [redacted]).”	higher in the lecanemab arm (mild: [redacted]; moderate: [redacted]) than the placebo arm (mild: [redacted]; moderate: [redacted]).”		
On page 125: “The EAG further requested a scenario analysis incorporating all grade 3+ AEs, all grade 2+ AEs of special interest (ARIA-E, ARIA-H, infusion-related reactions), and all grade 2+ AEs occurring in ≥5% of patients. The requested scenario was not provided. The company suggest that all AEs of special interest were already included.” On page 125: “The EAG requested an updated economic analysis including the associated rates for all AEs of special interest. In response, the company suggest that, given ARIA-E, ARIA-H, and infusion-related reactions were included, the CS is	The company propose the wording on page 125 is updated to read: “The EAG further requested a scenario analysis incorporating all grade 3+ AEs, all grade 2+ AEs of special interest (ARIA-E, ARIA-H, infusion-related reactions), and all grade 2+ AEs occurring in ≥5% of patients. The requested scenario was not provided. The company clarified that all AEs of special interest, irrespective of incidence and severity, were already included in the CS base-case.” “The EAG requested an updated economic analysis including the associated rates for all AEs of special interest. In response, the company clarified that, given ARIA-E,	The use of the word “suggested” is misleading. All AEs of special interest were included in the original CS model irrespective of incidence and severity, therefore the statement is inaccurate.	Not a factual inaccuracy. The first referenced text in the EAG report continues to explain that the impact of AEs on HRQoL was assumed captured and thus, were not explicitly modelled despite it being questionable whether the trial utilities adequately capture the HRQoL impact of AEs. For the second referenced text, while ARIA_E, ARIA-H, and infusion-related reactions were considered by the company, the EAG was referring to the use of isolated ARIA-H rates in the model, rather than overall rates.

already aligned with this request. Given the response, the request was seemingly misunderstood”	ARIA-H, and infusion-related reactions were included, the CS is already aligned with this request.”		
On page 129: “Clarification question B15 requested discussion regarding the plausibility of excluding AE disutilities and requested a scenario analysis whereby AE disutilities were incorporated into utility values. In response, the company acknowledge that, given the frequency of data collection, the full impact of AEs on HRQoL is not captured.”	The company propose the wording on page 129 is edited to read: “Clarification question B15 requested discussion regarding the plausibility of excluding AE disutilities and requested a scenario analysis whereby AE disutilities were incorporated into utility values. In response, the company acknowledge that, given the frequency of data collection, the full impact of AEs on HRQoL may not be captured.”	This is inaccurate. The wording used by the company in response to clarification question B15 was “*the company acknowledge that the frequency of data collection may mean the full impact of AEs is not captured*”.	Amended.
On page 137: “For AEs, there is lack of transparency as well as potential bias in how they are included in the model, and though the impact may be low, it might be worth exploring this further.”	The company propose the wording on page 137 is edited to read: “For AEs, there is potential bias in how they are included in the model, and though the impact may be low, it might be worth exploring this further.”	It is inaccurate that there is a lack of transparency in how AEs were included in the model. The criteria for AE inclusion are clearly laid out in the CS. As per the CS Section B.3.3.6, the criteria for selecting adverse	Not a factual inaccuracy. The EAG requested a full overview of AEs in Clarity AD, separated by severity for each treatment arm. This was never provided by the company.

		events for inclusion in the analysis were as follows: • Treatment-related incidence of grade 3+ AEs occurring in ≥5% patients in either treatment arm of Clarity AD, as is standard practice in HTAs. • ARIA-E, ARIA-H, and infusion-related reactions irrespective of incidence and severity, given these are AEs of special interest (AESIs).	

Issue 16 Typographical errors, formatting errors and minor text alterations

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
On page 13 (Table 1.1): “2.2 and 4.2”	The company propose the text on page 13 is edited to read: “2.1 and 4.2”	Typographical error.	Amended.
On page 15 and page 140:	The company propose the wording on page 15 and page 140 is edited to read:	The wording used by the EAG, “caregiver	Amended.

“Caregiver utility is modelled as the absolute quality of life (QoL) for both caregivers and patients summed in each cycle.”	“Modelling caregiver utility as the absolute QoL for both caregivers and patients summed in each cycle”	modelling is…”, implies that this approach was adopted in the base-case, rather than as a scenario. The proposed wording change aligns with the wording in the final bullet point “switching to natural history at…”.	
On page 15 and page 140: “The baseline age was set to 60 years”	The company propose the wording on page 15 and page 140 is edited to read: “Setting baseline age to 60 years”	The wording used by the EAG, “baseline age was set to…”, implies that this approach was adopted in the base-case, rather than as a scenario. The proposed change aligns with the wording in the final bullet point	Amend ed.

		"switching natural history to…".	
On page 15 (Table 1.2): "2.2 and 4.2"	The company propose the wording on page 15 is edited to read: "2.1 and 4.2"	Typographical error.	Amended.
On page 43: "Searches were conducted across a good range of databases and the company confirmed at clarification that "The same keywords were searched in all conference proceedings for all SLRs"."	The company propose the wording on page 43 is edited to read: "Searches were conducted across a good range of databases and the company confirmed at clarification that "*The same keywords were searched in all conference proceedings for all SLRs*"."	Formatting error – should be italicised to reflect other quotes in the document.	Amended.
On page 46 (Table 3.3): "Based on Adapted from Table 11 of the CS, Appendix D"	The company propose the wording on page 46 is edited to read: "Adapted from Table 11 of the CS, Appendix D"	Typographical error.	Amended.
On page 47: "The company confirmed that data on admission to full-time care were not collected in Clarity AD and noted that: *"Data on patient anxiety/depression is available from Clarity AD, as part of the EQ-5D-5L domains. Additionally, data on patient mood is available as part of the QOL-AD domains.""*	The company propose the wording on page 47 is edited to read: "The company confirmed that data on admission to full-time care were not collected in Clarity AD and noted that: *"Data on patient anxiety/depression is available from Clarity AD, as part of the EQ-5D-5L domains. Additionally, data on patient mood is available as part of the*	Missing reference.	The response to clarification (reference 10) was cited – no

	QOL-AD domains." (Response to clarification question A8):*"*		missing reference.
On page 48: "The CS (Section B.2.4.1) notes that:"	The company propose the wording on page 48 is edited to read: "The CS (Section B.2.3.1) notes that:"	Typographical error.	Amended.
On page 69: "…for overall ADCS-ADL-MCI, was 2.016 (95% CI: 1.208 to 2.843)"	The company propose the wording on page 69 is edited to read: "…for overall ADCS-ADL-MCI, was 2.016 (95% CI: 1.208 to 2.823)"	Typographical error.	Amended.
On page 74: "(i.e., participants with MCI due to AD who were without symptomatic AD medication at baseline and participants with mild dementia due to AD who were without memantine treatment at baseline.	The company propose the wording on page 74 is edited to read: "(i.e., participants with MCI due to AD who were without symptomatic AD medication at baseline and participants with mild dementia due to AD who were without memantine treatment at baseline**)**."	Typographical error. Closed bracket to be added.	Amended.
On page 78: "In the ITT FAS+ population, the majority of subjects were *ApoE4* carriers ([redacted]% of which [redacted]% were heterozygous *ApoE4* carriers and [redacted]% were homozygous *ApoE4* carriers, therefore greater variability of outcomes is expected in this smaller group due to reduced patient numbers."	The company propose the wording on page 78 is edited to read: "In the ITT FAS+ population, the majority of subjects were *ApoE4* carriers ([redacted]% of which [redacted]% were heterozygous *ApoE4* carriers and [redacted]% were homozygous *ApoE4* carriers, therefore greater variability of outcomes is	Typographical error.	Amended.

	expected in this smaller group due to reduced patient numbers**)**."		
On page 83: "The company provided the following results (Table 3.28) for Study 210"	The company propose the wording on page 83 is edited to read: "The company provided the following results (Table 3.28) for Study 201"	Typographical error.	Amended.
On page 86: "the incidences of AE of special interest (ARIA-E, ARIA-H and infusion-related reactions were [redacted]"	The company propose the wording on page 86 is edited to read: "the incidences of AE of special interest (ARIA-E, ARIA-H and infusion-related reactions**)** were [redacted]"	Typographical error. Closed bracket to be added.	Amended.
On page 86: "The majority (81%) of ARIA-E cases resolving by four months since onset"	The company propose the wording on page 86 is edited to read: "The majority (81%) of ARIA-E cases resolved by four months since onset"	Typographical error.	Amended.
On page 86: "No differences (>5%) were reported for mortality or 'other 'SAEs' (serious adverse events)"	The company propose the wording on page 86 is edited to read: "No differences (>5%) were reported for mortality or other 'SAEs' (serious adverse events)"	Typographical error. Double open apostrophe to be removed.	Amended.
On page 86: "The EAG notes that the incidence TEAEs leading to the interruption…"	The company propose the wording on page 86 is edited to read:	Typographical error.	Amended.

	“The EAG notes that the incidence of TEAEs leading to the interruption…”		
On page 87: “ARIA-E (12.6% versus 1.7%) [redacted].”	The company propose the wording on page 87 is edited to read: “ARIA-E (12.6% versus 1.7%) [redacted].”	Typographical error.	Amended.
On page 88 (Table 3.34), descriptive text on pages 86 and 87, and on page 98 (Table 3.48): “Infusion-related reaction”	The company propose the wording on pages 86-88 and 98 is edited to read: “Infusion related reaction”	Typographical error. There is a distinction provided by the hyphen. Infusion-related reactions with hyphen is the overall AE term, which includes the MedDRA preferred terms ‘infusion related reaction’ and ‘infusion site reaction’.	Amended.

On page 90: "The CS noted that most (lecanemab ([redacted]); placebo ([redacted]) AEs of special interest"	The company propose the wording on page 90 is edited to read: "The CS noted that most (lecanemab [[redacted]; placebo [[redacted]**)** AEs of special interest"	Typographical error. Closed bracket to be added.	Amend ed.
On page 90 (Table 3.36) and page 99, (Table 3.49): "ARIA-H Macrohaemorrhage Superficial siderosis Cerebral microhaemorrhage"	The company propose the wording on pages 90 and 99 is edited to read: "ARIA-H Macrohaemorrhage Superficial siderosis Cerebral microhaemorrhage"	Minor text alteration for clarity. The sub-categories of ARIA-H should be indented.	Amend ed.
On page 91: *"…the incidence of serious ARIA-E was [redacted] in the lecanemab arm; there were [redacted] in the placebo arm*." The data described in Table 3.36 are not consistent with these descriptions where severe (serious) ARIE-E events in the lecanemab group have an incidence of [redacted]."	The company propose that the following sentence on page 91 is removed: "The data described in Table 3.36 are not consistent with these descriptions where severe (serious) ARIE-E events in the lecanemab group have an incidence of [redacted]".	Statement is incorrect. Serious and severe TEAEs have different definitions. Table 25 of the CS, Document B presents both serious and severe AEs separately indicating that they are not the same.	Amend ed.

		Severe AEs (CSR, section 9.5.1.4.1.1)[5] are defined as AEs that are "Incapacitating, with inability to work or to perform normal daily activity". A serious adverse event (CSR section 9.5.1.4.3)[5] was defined as any untoward medical occurrence that at any dose: • Resulted in death • Was life-threatening (ie, the subject was at immediate risk of death from	

		the AE as it occurred; this did not include an event that, had it occurred in a more severe form or was allowed to continue, might have caused death) • Required inpatient hospitalisation or prolongation of existing hospitalisation • Resulted in persistent or significant	

		disability/incapacity • Was a congenital anomaly/birth defect (in the child of a subject who was exposed to the study drug)	
On page 91 (Table 3.38): "Based on Adapted from Table 28[2]"	The company propose the wording on page 91 is edited to read: "Based on Adapted from Table 28[2], CS"	Minor text alteration for consistency.	Amended.
On page 92: "The Cs also states that *"most cases of ARIA-H…""*	The company propose the wording on page 92 is edited to read: "The CS also states that *"most cases of ARIA-H…""*	Typographical error.	Amended.
On page 93: "The CS states *"that most cases of ARIA-H…""*	The company propose the wording on page 93 is edited to read: "The CS states that *"most cases of ARIA-H…""*	Typographical error.	Amended.
On page 93:	The company propose the wording on page 93 is edited to read:	Typographical error.	Amended.

"*All cases of microhaemorrhage with leacanemab or placebo were ongoing"*	"*All cases of microhaemorrhage with lecanemab or placebo were ongoing"*		
On page 93: "Table 3:41 indicates the time to onset of ARIA-H"	The company propose the wording on page 93 is edited to read: "Table 3.41 indicates the time to onset of ARIA-H"	Typographical error.	Amended.
On page 93: "Isolated ARIA-H events were similar between groups, overall and by maximum radiographic severity, (Table 3:42)"	The company propose the wording on page 93 is edited to read: "Isolated ARIA-H events were similar between groups, overall and by maximum radiographic severity, (Table 3.42)"	Typographical error.	Amended.
On page 94: "Overall rates of concurrent ARIA-E and ARIA-H (Table 3:43)"	The company propose the wording on page 94 is edited to read: "Overall rates of concurrent ARIA-E and ARIA-H (Table 3.43)"	Typographical error.	Amended.
On page 99: "Searches conducted in August 2013 were transparent…"	The company propose the wording on page 99 is edited to read: "Searches conducted in August 2023 were transparent…"	Typographical error.	Amended.
On page 100: "…hence the pooled treatment effects did not differ substantially the results of Clarity AD"	The company propose the wording on page 100 is edited to read:	Minor text alteration for clarity.	Amended.

	"…hence the pooled treatment effects did not differ substantially from the results of Clarity AD"		
On page 101: "Further information, on the different rates symptomatic AD treatment in study participants"	The company propose the wording on page 101 is edited to read: "Further information, on the different rates of symptomatic AD treatment in study participants"	Minor text alteration for clarity.	Amend ed.
On page 101: "[redacted], relative to expectations for the UK"	The company propose the wording on page 101 is edited to read: "[redacted], relative to expectations for the UK"	Typographical error. Closed bracket to be added.	Amend ed.
On page 110: "…it was also noted by the clinical expert, that in UK practice, staging of AD is nearly always subjective, relying on clinical experience and diagnostic criteria (e.g., Diagnostic and Statistical Manual of Mental Disorders (DSM),29 NIA-AA30) rather than specific staging tools (such as CDR-SB)."	The company propose the wording on page 110 is edited to read: "…it was also noted by the clinical expert, that in UK practice, staging of AD is nearly always subjective, relying on clinical experience and diagnostic criteria (e.g., Diagnostic and Statistical Manual of Mental Disorders (DSM),29 NIA-AA30) rather than specific staging tools (such as CDR-SB)."	This is misleading, as it does not acknowledge that MMSE is also not used in clinical practice. Wording to be amended to "CDR-SB and MMSE".	Amend ed.
On page 112: "(according to CS Table 70 the ICER for the mild AD subgroup is substantially higher than	The company propose the wording on page 112 is edited to read: "(according to CS Table 70 the list price ICER for the mild AD subgroup is substantially higher	Minor text alteration to clarify that these are list price ICERs, given that EAG	Amend ed.

for the MCI subgroup [redacted] versus [redacted] respectively)"	than for the MCI subgroup [redacted] versus [redacted] respectively)"	preferred base-case analysis (Table 1.23) is based on the PAS price.	
On page 113: "The model has a 45 -year time horizon which is effectively lifetime".	The company propose the wording on page 113 is edited to read: "The model has a 30-year time horizon which is effectively lifetime".	This is incorrect. The model has a 30-year time horizon.	Amend ed
On page 114 (Table 4.8): The value of monthly transition probabilities from MCI to mild AD is given as "[redacted]%"	The company requests the value in the table to be rounded up to [redacted]% given that the full value is [redacted]%.	Incorrect value is presented in the table.	Amend ed.
On page 118: "The company explained that backward transitions were consistent with half of the IPECAD models and were deemed appropriate giving that the model has a short cycle length of one month, and that such backward transitions were likely to be temporary."	The company propose the wording on page 118 is edited to read: "The company explained that backward transitions were consistent with half of the IPECAD models and were deemed appropriate given that the model has a short cycle length of one month, and that such backward transitions were likely to be temporary."	Typographical error.	Amend ed.
On page 122: "In clarification question B9.e, the company was asked why the mortality rates have not been informed by Potashman et al. annual	The company propose the wording on page 122 is edited to read: "In clarification question B9.e, the company was asked why the mortality rates have not been	Typographical error.	Amend ed.

transition probabilities to death from each health state.pot[32]"	informed by Potashman et al. annual transition probabilities to death from each health state.[32]"		
On page 125: "The prevalence of mild and moderate TEAEs (n(%)) was significantly higher in the lecanemab arm (mild: [redacted]); moderate: [redacted]) than the placebo arm (mild: [redacted]; moderate: [redacted])."	The company propose the wording on page 125 is edited to read: The prevalence of mild and moderate TEAEs (n(%)) was significantly higher in the lecanemab arm (mild: [redacted]); moderate: [redacted]) than the placebo arm (mild: [redacted]; moderate: [redacted]).	Incorrect value reported.	Amended.
On page 125: "To avoid double-counting, rates of isolated ARIA-H rates and treatment-emergent rates were used to incorporate AEs of special interest."	The company propose the wording on page 125 is edited to read: "Rates of isolated ARIA-H were used to avoid double-counting, given ARIA-H can occur concurrently with ARIA-E. Treatment-emergent rates were used given the natural occurrence of ARIA-H in AD patients."	For alignment with the wording employed in the CS (page 128) and for clarity in the description of methodology.	Amended.
On page 127 (Table 4.14): "Decrement between health state values derived from Farina et al. 2020)"	The company propose the wording on page 127 is edited to read: "Decrement between health state values derived from Farina et al. **(**2020)"	Typographical error. Open bracket to be added.	Amended.
On page 127: "To incorporate the impact of caregivers, caregiver disutilities were derived from Black et	The company propose the wording on page 127 is edited to read: "To incorporate the impact on caregivers, caregiver disutilities were derived from Black et	Typographical error.	Amended.

al. 2018[41] and applied to health state utility values."	al. 2018[41] and applied to health state utility values."		
On page 129: "In conclusion, the effect of institutionalisation on caregiver utilities is unclear and the EAG disables the utility decrement in a scenario."	The company propose the wording on page 129 is edited to read: "In conclusion, the effect of institutionalisation on caregiver utilities is unclear and the EAG disables the utility decrement in its base case."	Minor text alteration for clarity that this is in the EAG preferred base case, not a scenario.	Amended.
On page 138: "Increased QALYs for lecanemab by increasing the number of patients staying at the MCI community stage, through slower disease progression and treatment-dependent utilities (QALY gain 0.73)."	The company propose the wording on page 138 is edited to read: "Increased QALYs for lecanemab by increasing the number of patients staying at the MCI and mild community stage, through slower disease progression and treatment-dependent utilities (QALY gain 0.73)."	Textual clarification. Lecanemab delays progression for patients with MCI due to AD and mild AD.	Amended.
On page 138: "The original submission included transition probabilities from Potashman et al. as they were reported in Herring et al, which calculated an AD 'landing spot' distribution for patients leaving the MCI due to AD health state, requiring an additional calculation step that was not needed when using the probabilities directly	The company propose the wording on page 138 is edited to read: "The original submission included transition probabilities derived from Potashman et al. as they were reported in Herring et al, which calculated an AD 'landing spot' distribution for patients leaving the MCI due to AD health state, requiring an additional calculation step that was not needed when using the probabilities directly	Minor textual clarification.	Amended.

from Potashman et al, according to the company.”	from Potashman et al, according to the company.”		
On page 138 (Table 5.1)	The company requests the Total QALYs data in the table be amended to: [redacted] for SoC [redacted] for lecanemab [redacted] for incremental vs. SoC	Incorrect values reported in Table 5.1	The additional row with wrong values has been deleted.
On page 139: “The company updated the economic model using 81-week patient count data for health states using CDR-SB and global CDR (scenario analysis only).”	The company propose the wording on page 139 is edited to read: “The company updated the economic model using week-81 patient count data for health states using CDR-SB and global CDR (scenario analysis only).”	Minor text alteration for clarity and alignment with the CS and clarification question response.	Amended.
On page 139: “The original submission used 79-weeks patient count for the 0-18 months transitions.”	The company propose the wording on page 139 is edited to read: “The original submission used week-79 patient count for the 0-18 months transitions.”	Minor text alteration for clarity and alignment with the CS and clarification	Amended.

		question response.	
On page 139: “According to the company, the 81-week count is more reflective of the ITT FAS+ population, as some patients had their final visit more than one week later than the protocol specified.”	The company propose the wording on page 139 is edited to read: “According to the company, the week-81 count is more reflective of the ITT FAS+ population, as some patients had their final visit more than one week later than the protocol specified.”	Minor text alteration for clarity and alignment with the CS and clarification question response.	Amend ed.

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1. Petersen RC, Aisen PS, Andrews JS, Atri A, Matthews BR, Rentz DM, et al. Expectations and clinical meaningfulness of randomized controlled trials. Alzheimers Dement J Alzheimers Assoc. 2023 Feb 7;

2. Liu KY, Schneider LS, Howard R. The need to show minimum clinically important differences in Alzheimer’s disease trials. Lancet Psychiatry. 2021 Nov;8(11):1013–6.

3. Andrews JS, Desai U, Kirson NY, Zichlin ML, Ball DE, Matthews BR. Disease severity and minimal clinically important differences in clinical outcome assessments for Alzheimer's disease clinical trials. Alzheimers Dement N Y N. 2019;5:354–63.

4. Lansdall CJ, McDougall F, Butler LM, Delmar P, Pross N, Qin S, et al. Establishing Clinically Meaningful Change on Outcome Assessments Frequently Used in Trials of Mild Cognitive Impairment Due to Alzheimer's Disease. J Prev Alzheimers Dis. 2023;10(1):9–18.

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Appendix A

Table 1: Cost and resource use comparison between the company's economic model and the NHS England Alzheimer's MCI model.

Cost/resource use	Company model	Reference	NHS England Alzheimer's MCI model	Reference in NHSE model
Unit cost lecanemab IV infusion administration per visit	£207.59	National Schedule of NHS Costs 2021/22 (Deliver Simple Parenteral Chemotherapy at First Attendance, outpatient, SB12Z)	£565.00	NR*
Unit cost lumbar puncture	£295.80	National Schedule of NHS Costs 2021/22 (Outpatient procedure diagnostic spinal puncture, 19 years and over, neurology service, HC72A, service code 401)	£580.00	"[redacted], 16 Oct 2023 email"
Unit cost PET-CT	£396.94	National Schedule of NHS Costs 2021/22, weighted average of outpatient PET scan (RN01A, RN07A)	£1000.00	"[redacted] email 15/08/23"

Aβ testing: ratio CSF:PET CT	90%:10%	Clinical opinion. UK HTA advisory board, July 2023	85%:15%	NR
MRI safety monitoring	Average of 3.88 MRIs in year 1 and 1.13 in years 2, 3, and 4	UK HTA advisory board report. July 2023.	MRIs in intervals of 13 weeks	"[redacted], 16 Oct 23 email"
GP visit	Not included	N/A	3 visits (total cost of £75.00)	NR
Quarterly outpatient review	Not included	N/A	Every 13 weeks (£350 each)	NR
ApoE4 test	Not included	N/A	Unit cost of £250	NR
		N/A	Outpatient appointment: unit cost of £200	NR
		N/A	Counselling: unit cost of £350	NR
Referral to local services (e.g., memory clinics)	Not included	N/A	Unit cost: £400	NR

Adapted from EAG report Table 4.18
**NHSE reference WD02Z (Alzheimer's Disease or Dementia, treated by a Non-Specialist Mental Health Service Provider), however, the unit costs used in the model does not align with any of the costs under code WD02Z in National Schedule of NHS Costs 2021/22.*
APoE4 = apolipoprotein E4; CSF = cerebrospinal fluid; GP = general practitioner; IV = intravenous; MCI = mild cognitive impairment; MRI = magnetic resonance imaging; N/A = not applicable; NHS = National Health Service; NR = not reported; PET-CT = positron emission tomography computed tomography