Medicinrådet

Bilag til Medicinrådets vurdering af lecanemab til patienter med let kognitiv svækkelse og let demens som følge af Alzheimers sygdom

Vers. 1.0

Bilagsoversigt

1. Ansøgers notat til Rådet vedr. lecanemab
2. Forhandlingsnotat fra Amgros vedr. lecanemab
3. Ansøgers endelige ansøgning vedr. lecanemab

Eisai comments on the Danish Medicines Council (DMC) assessment report of lecanemab for the treatment of mild cognitive impairment due to Alzheimer's disease (AD) or mild Alzheimer's disease (Early Alzheimer's disease) that are apolipoprotein E ε4 non-carriers or heterozygotes

Eisai would like to thank the DMC and acknowledge the significant work that the DMC has done during the assessment. We would like to emphasize the clear alignment we share regarding the interpretation of the data and its integration into the health economic model. At the same time, we would like to clarify a few points where our perspectives differ, particularly in relation to certain assumptions in the health economic model and the clinical meaningfulness of lecanemab treatment.

Treatment effect after discontinuation

The assumptions made by the DMC regarding a complete loss of treatment effect immediately after discontinuation significantly influence the ICER, resulting in a considerably higher ICER assumed by the DMC compared to the estimate calculated by Eisai.

In the assessment report, the DMC assumed that all lecanemab treatment effect is lost immediately after treatment discontinuation, based on findings from Study 201, a double-blind, phase II trial comparing lecanemab with placebo. While Study 201 was a robust clinical trial, it would not be appropriate to use it as the basis for determining the treatment effect of lecanemab after discontinuation for patients in Clarity AD. Study 201 included a considerably smaller sample size than Clarity AD, which inherently limits the robustness of some conclusions drawn by the DMC.

We agree with the DMC that Clarity AD cannot elucidate whether there is an effect of lecanemab after treatment discontinuation. However, clinical experts as well as a NICE evaluation committee have noted that it is highly implausible that the effect on disease progression will disappear immediately after stopping treatment with lecanemab[1], which is the assumption taken by the DMC. Rather, the level of treatment effect is expected to diminish gradually over time.

Lecanemab slows disease progression by reducing the levels of toxic amyloid protofibrils and plaques in the brains of individuals with AD. Data demonstrates that after treatment discontinuation, amyloid and other biomarkers require time to reaccumulate and gradually revert back towards pre-treatment levels. Therefore, it is reasonable to assume some level of residual treatment effect after the treatment has been discontinued. For example, it is estimated to take approximately:

- 2 years for patients who have received at least 18 months of lecanemab treatment to again surpass the 30 CL threshold for "amyloid PET positivity", and 11 years for patients' amyloid PET levels to revert back to 50 CLs. The published literature identifies that patients with amyloid levels at or below 50 CLs experience little to no clinical progression within the subsequent 3.4 – 4.5 years of assessment[2,3,4]

In summary, while Eisai acknowledges the substantial uncertainty in determining the level of residual treatment effect after treatment discontinuation, the DMC assumption that all treatment effect is lost immediately is not considered clinically plausible. As an alternative to the DMC assumption, Eisai considers that a treatment waning period of 11 years can be applied in the cost-effectiveness model. This would be applied after 18 months of treatment, as the loss of treatment effect for the first 18 months is already considered by using a control-based multiple imputation approach as requested by EMA[5].

Time To Discontinuation (TTD) and Time To Worsening (TTW) alignment:

Since data from Clarity AD (core) is used to estimate the TTW Hazard Ratio (copy increments combined approach), it would be appropriate to use the same data point (18 months) for TTD to maintain consistency in the sources of data used. In the DMC assessment, data from Clarity AD (core) is used to estimate the TTW Hazard Ratio, while data from the open label extension (OLE) is used for TTD.

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[1] https://www.nice.org.uk/guidance/gid-ta11220/documents/674

[2] van der Kall LM 2021 et al., Association of β-Amyloid Level, Clinical Progression, and Longitudinal Cognitive Change in Normal Older Individuals. Neurology. 96(5):e662-e670.

[3] Sperling RA, 2024 et al., Amyloid and Tau Prediction of Cognitive and Functional Decline in Unimpaired Older Individuals: Longitudinal Data from the A4 and LEARN Studies. J Prev Alzheimers Dis. 11(4):802-813.

[4] Quenon L, 2024 et al., AMYPAD Consortium. Amyloid-PET imaging predicts functional decline in clinically normal individuals. Alzheimers Res Ther. 16(1):130.

[5] Copy increments approach to measure changes from baseline, where values from the placebo group were used to impute missing values in the lecanemab group

Transitions from MCI due AD and Mild AD to Severe AD

While we acknowledge the DMC's concern regarding observed transitions, we believe the base-case modelling approach reflects the most rigorous interpretation of the available trial data. The absence of both MCI due to AD and Mild AD to Severe AD transitions in the lecanemab arm over 18 months (0 events vs. 4 in placebo) represents clinically meaningful evidence that should not be dismissed. The DMC's comparison to mortality differences mixes distinct clinical endpoints. Death represents a rare event with a high and random variation, whereas disease progression is the primary outcome measure with a substantially larger event count. Assuming identical transition probabilities between arms despite observed differences in the trial data contradicts the principle of evidence-based modelling and effectively invalidates a key clinical benefit observed in the trial up to that point. The DMC's approach of imposing equal transition rates between arms is not based on any empirical justification and systematically underestimates the treatment benefit in a manner inconsistent with the observed trial outcomes.

Stage-specific utility values

The statistically significant EQ-5D-5L difference at 18 months (1.8 points, 95% CI: 0.31 – 3.34) reported in Clarity AD represents a real gain in patient-reported quality of life (QoL) that should be captured in the economic evaluation. The DMC's distinction between "delayed progression" and "treatment effect" is artificial since delayed progression is the treatment benefit, and patients can experience improved QoL regardless of the mechanism. Using both stage and treatment specific utilities better reflects the trial's evidence showing that lecanemab patients maintain better functioning even within the same nominal stage, directly modelling observed clinical benefits into QALYs as recommended by health economic guidelines.

This position is further contradicted by the DMC's assumption of identical MCI due to AD and Mild AD to Severe AD transition rates between arms (discussed above). If lecanemab provides no progression benefit at that stage, as the DMC assumes, then the observed EQ-5D-5L difference at 18 months cannot be attributed to delayed disease progression and must represent a direct treatment effect on QoL. It would be unjustified to simultaneously deny progression benefits while rejecting QoL improvements as merely reflecting delayed progression.

Updated ICER

[redacted]

Clinical meaningfulness

In the assessment report, DMC state that lecanemab does not meet minimal clinically important difference (MCID) thresholds for CDR-SB, quoting a MCID of +1 for MCI due to AD and +2 for Mild AD patients, based on a recent systematic literature review. Other publications have suggested a CDR-SB MCID of 0.98 for MCI due to AD and 1.63 for Mild AD patients, measured over approximately one year[6]. However, it is important to also note that these values represent individual-level change and not group-level comparative change. Both MCID authors and the EU-US CTAD Task Force explicitly discourage applying within-patient MCIDs to group-level differences[7]. Furthermore, studies reporting MCIDs in dementia differ substantially from the lecanemab target population—they often do not confirm elevated amyloid levels or apply current diagnostic criteria for MCI due to AD and Mild AD dementia—leading to potential misinterpretation of outcomes. Accordingly, applying these MCID values as benchmarks for clinical significance in Clarity AD is questionable and warrants careful consideration.

In the context of the lecanemab Clarity AD trial, benchmarking the mean change from baseline of 0.58 (a group-level difference) against within-patient MCIDs reported in the literature is a methodologically flawed approach. Given that the placebo arm declined by 1.73 points, this would imply lecanemab must show virtually no decline over 18 months to meet such thresholds. Interpreting clinical meaningfulness as requiring an 11-month delay in progression (≈60% slowing) is unrealistic and sets an implausible standard for any innovative therapy for AD, whether currently marketed or in development. Applied to a time-saved analysis, for Mild AD patients, even a 17-month delay over an 18-month period—equivalent to a 95% slowing or near-complete halt of disease progression—would still fail to meet the proposed threshold for meaningful benefit. This illustrates how such criteria set an implausible and unrealistic standard for evaluating innovative therapies[8].

[6] Andrews JS, 2019 et al., Disease severity and minimal clinically important differences in clinical outcome assessments for Alzheimer's disease clinical trials. Alzheimers Dement (N Y). 2019;5:354-363

[7] Angioni D, 2024 et al., Clinical Meaningfulness in Alzheimer's Disease Clinical Trials. A Report from the EU-US CTAD Task Force. *J Prev Alzheimers Dis*. 11(5):1219-1227.

[8] Lanctot K, 2025 et al., Measuring time saved in Alzheimer's disease: What is a meaningful slowing of progression? *Alzheimers Dement (N Y)*. 11(2):e70081.

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21.11.2025

DBS/LSC

Forhandlingsnotat

Dato for behandling i Medicinrådet	17.12.2025
Leverandør	Eisai
Lægemiddel	Leqembi (lecanemab)
Ansøgt indikation	Behandling af voksne patienter med klinisk diagnosticeret let kognitiv svækkelse og let demens som følge af Alzheimers sygdom (tidlig Alzheimers sygdom), som ikke er bærere af apolipoprotein E ε4 (ApoE ε4) eller er heterozygote, og som har bekræftet amyloid patologi
Nyt lægemiddel / indikationsudvidelse	Nyt lægemiddel

Prisinformation

Amgros har forhandlet følgende pris på Leqembi (lecanemab):

Tabel 1: Forhandlingsresultat [redacted]

Lægemiddel	Styrke (pakningsstørrelse)	AIP (DKK)	Forhandlet SAIP (DKK)	Forhandlet rabat ift. AIP
Leqembi	100 mg/ml (2ml)	2.313,81	[redacted]	[redacted]
Leqembi	100 mg/ml (5 ml)	4.590,30	[redacted]	[redacted]

[redacted]

[redacted]

[redacted]

Tabel 2: [redacted]

[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

Tabel 3: Forhandlingsresultat [redacted]

Lægemiddel	Styrke (pakningsstørrelse)	AIP (DKK)	Forhandlet SAIP (DKK)	Forhandlet rabat ift. AIP
[redacted]				
Leqembi	100 mg/ml (2ml)	2.313,81	[redacted]	[redacted]
Leqembi	100 mg/ml (5 ml)	4.590,30	[redacted]	[redacted]
[redacted]				
Leqembi	100 mg/ml (2 ml)	2.313,81	[redacted]	[redacted]
Leqembi	100 mg/ml (5 ml)	4.590,30	[redacted]	[redacted]
[redacted]				
Leqembi	100 mg/ml (2 ml)	2.313,81	[redacted]	[redacted]
Leqembi	100 mg/ml (5 ml)	4.590,30	[redacted]	[redacted]

Pristilbuddene er betinget af Medicinrådets anbefaling. Det betyder at hvis Medicinrådet ikke anbefaler Leqembi, indkøbes lægemidlet til AIP.

Aftaleforhold

[redacted]

[redacted]

[redacted]

[redacted]

Informationer fra forhandlingen

[redacted]

[redacted]

Konkurrencesituationen

Leqembi er første potentielle behandlingsmulighed til Alzheimers i Danmark. Kisunla (donanemab) til samme indikation er i proces i Medicinrådet og vurderingen forventes afsluttet i maj 2026.

Tabel 4 viser den årlige lægemiddeludgift for behandling med Leqembi. Lægemiddeludgiften er beregnet for en gennemsnitlig patient med en vægt på 70 kg., jf. CLARITY-AD studiet, dvs. ved forbrug af en 2 ml og en 5 ml pakning. [redacted]

Tabel 4: Sammenligning af lægemiddeludgifter pr. patient for behandling med Leqembi

[redacted]	Lægemiddel	Styrke (pakningsstørrelse)	Dosering	Pris pr. pakning* (SAIP, DKK)	Lægemiddeludgift pr. år (SAIP, DKK)
[redacted]	Leqembi	100 mg/ml (2 ml) 100 mg/ml (5 ml)	10 mg/kg hver 2. uge, i.v.	[redacted]	[redacted]
[redacted]	Leqembi	100 mg/ml (2 ml) 100 mg/ml (5 ml)	10 mg/kg hver 2. uge, i.v.	[redacted]	[redacted]
[redacted]	Leqembi	100 mg/ml (2 ml) 100 mg/ml (5 ml)	10 mg/kg hver 2. uge, i.v.	[redacted]	[redacted]

*Prisen pr. mg for de to pakningsstørrelser er forskellig. Da Leqembi gives vægtbaseret betyder det, at man skal være ekstra opmærksom på at anvende den eller de pakningsstørrelser, som bedst matcher patientens dosis.

Status fra andre lande

Tabel 5: Status fra andre lande

Land	Status	Link
Norge	Under vurdering	Link til status
England	Under vurdering	Link til status
Sverige	Under vurdering	Link til status

Opsummering

[redacted]

[redacted]

Application for the assessment of lecanemab (Leqembi®) for the treatment of mild cognitive impairment due to Alzheimer's disease or mild Alzheimer's disease that are apolipoprotein E ε4 non-carriers or heterozygotes

Color scheme for text highlighting	
Color of highlighted text	Definition of highlighted text
	Confidential information

Contact information

Contact information	
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Tables and Figures

Abbreviations

Abbreviation	Definition	Abbreviation	Definition
Aβ	Amyloid beta/amyloid-β	IRR	Infusion related reaction

AChEI	Acetylcholinesterase inhibitor	ITT	Intent to treat
AD	Alzheimer's disease	IV	Intravenous
ADA	Antidrug antibodies	KM	Kaplan Meier
ADAS-cog14	Alzheimer's Disease Assessment Scale – Cognitive Subscale 14	KOL	Key opinion leader
ADCS MCI-ADL	Alzheimer's Disease Cooperative Study-Activities of Daily Living Inventory Mild Cognitive Impairment Version	LY	Life years
ADL	Activities of Daily Living	MCI	Mild cognitive impairment
ADNI	Alzheimer's Disease Neuroimaging Initiative	MedDRA	Medical Dictionary for Regulatory Activities
ADRC	Alzheimer's Disease Research Centers	MMSE	Mini-Mental State Exam
AE	Adverse event	MoCA	Montreal Cognitive Assessment
AESI	Adverse event of special interest	MRI	Magnetic resonance imaging
ApoE	Apolipoprotein E	NACC	National Alzheimer Coordinating Center
ApoE ε4	Apolipoprotein E4	NfL	Neurofilament light chain
APP	Amyloidogenic pathway	NFT	Neurofibrillary tangles
ARIA	Amyloid-related imaging abnormalities	NIA-AA	National Institute of Aging - Alzheimer Association
ARIA-E	Amyloid related imaging abnormalities with edema or effusion	NACC-USD	National Alzheimer's Coordinating Center Uniform Data Set
ARIA-H	Amyloid related imaging abnormalities with hemosiderin deposition	NMDA	N-methyl-D-aspartate
AT(N)	Amyloid, tau, and neurodegeneration criteria	OLE	Open-label extension
BACE	β-Site amyloid precursor protein cleaving enzyme 1	PET	Positron Emission Tomography
BMI	Body mass index	PK	Pharmacokinetic(s)
CAA	Cerebral amyloid angiopathy	PSA	Probabilistic sensitivity analysis
CDR	Clinical Dementia Rating	p-tau	Phosphorylated tau
CDR-SB	Clinical Dementia Rating - Sum of Boxes	QALY	Quality-adjusted life year
CEM	Cost effectiveness model	QoL	Quality of life
CHMP	Committee for Medicinal Products for Human Use	QOL-AD	Quality of life in Alzheimer's Disease
CI	Confidence interval	RUDAS	Rowland Universal Dementia Assessment Scale
CPI	Consumer Price Index	SAE	Serious adverse event
CSF	Cerebrospinal fluid	SAS	Safety analysis set
CSR	Clinical study report	SC	Subcutaneous
CT	Computed tomography	SD	Standard deviation

CTCAE	Common Terminology Criteria for Adverse Event	SE	Standard error
DES	Discrete event simulation	SLR	Systematic literature review
DRG	Diagnosis related group	SoC	Standard of care
DSA	Deterministic sensitivity analysis	SmPC	Summary of product characteristics
ECG	Electrocardiogram	SUVr	Standard uptake-value ratio
EMA	European Medicines Agency	TEAE	Treatment emergent adverse event
FAS+	Full analysis set+	TESAE	Treatment-emergent serious adverse event
FDA	Food and Drug Administration	TP	Transition Probabilities
GPB	British Pound Sterling	TTW	Time to worsening
HR	Hazard ratio	UK	United Kingdom
HRQoL	Health-related quality of life	US	United States
HTA	Health technology assessment	VAS	Visual analogue scale
IADL	Instrumental Activities of Daily Living	vMRI	Volumetric magnetic resonance imaging
ICER	Incremental cost effectiveness ratio	WMS-IV LMII	Wechsler Memory Scale-IV Logical Memory II
IgG1	Immunoglobulin G1	ZBI	Zarit Burden Interview

1. Regulatory information on the medicine

Overview of the medicine	
Proprietary name	Leqembi®
Generic name	Lecanemab
Therapeutic indication as defined by EMA	Lecanemab is indicated for the treatment of adult patients with a clinical diagnosis of mild cognitive impairment and mild dementia due to Alzheimer's disease (Early Alzheimer's disease) who are apolipoprotein E ε4 (ApoE ε4) non-carriers or heterozygotes with confirmed amyloid pathology (1).
Marketing authorization holder in Denmark	Eisai AB
ATC code	N06DX04 (1)
Combination therapy and/or co-medication	Given as monotherapy (1)
(Expected) Date of EC approval	15 April 2025
Has the medicine received a conditional marketing authorization?	No
Accelerated assessment in the European Medicines Agency (EMA)	No
Orphan drug designation (include date)	No

Overview of the medicine	
Other therapeutic indications approved by EMA	N/A
Other indications that have been evaluated by the DMC (yes/no)	No
Joint Nordic assessment (JNHB)	Are the current treatment practices similar across the Nordic countries (DK, FI, IS, NO, SE)? No Is the product suitable for a joint Nordic assessment? No If no, why not? Country-specific dossier already submitted in Sweden
Dispensing group	BEGR
Packaging – types, sizes/number of units and concentrations	Leqembi® (lecanemab) 100 mg/mL concentrate for solution for infusion. Available as (1): one vial of 2 mL; 200 mg of lecanemab and one vial of 5 mL; 500 mg of lecanemab

2. Summary table

Summary	
Therapeutic indication relevant for the assessment	Lecanemab is indicated for the treatment of adult patients with a clinical diagnosis of mild cognitive impairment and mild dementia due to Alzheimer's disease (Early Alzheimer's disease) who are apolipoprotein E ε4 (ApoE ε4) non-carriers or heterozygotes with confirmed amyloid pathology (1).
Dosage regiment and administration	The recommended dose of lecanemab is 10 mg/kg administered as an intravenous (IV) infusion biweekly (1). [redacted]
Choice of comparator	Placebo (IV) + standard of care (acetylcholinesterase inhibitors + N-methyl-D-aspartate receptor antagonist)
Prognosis with current treatment (comparator)	At present, pharmacological treatment is comprised of symptomatic treatment such as acetylcholinesterase inhibitors (donepezil, galantamine, rivastigmine) and N-methyl-D-aspartate receptor antagonist (memantine) (2). These treatments provide temporary reduction in symptoms, but do not treat the underlying cause of AD, nor delay disease progression (2).
Type of evidence for the clinical evaluation	Clarity AD (Randomised Phase III head-to-head 'Core Study' and Clarity AD OLE using comparator natural history cohort.
Most important efficacy endpoints (Difference/gain compared to comparator)	Difference in adjusted least-squares mean change in from baseline at 18 months in Clinical Dementia rating – Sum of Boxes (CDR-SB) for lecanemab vs placebo: −0.58; 95% confidence interval [CI], −0.81 to −0.35; p<0.001. Reduction in amyloid burden compared to placebo, with a mean change from baseline of -55.541 CL for lecanemab vs 3.895 CL for placebo (mean change from baseline: -59.437 CL; p<0.00001) (3).
Most important serious adverse events for the intervention and comparator	Symptomatic ARIA-H reported in 0.8% [redacted] for the lecanemab group and [redacted] for the placebo group. Symptomatic ARIA-E reported in [redacted] for the lecanemab group and [redacted] in the placebo group.

Summary	
	Macrohaemorrhage reported in lower than [redacted] in placebo group and [redacted] in the lecanemab group.
Impact on health-related quality of life	Clinical documentation: EQ-5D-5L, patient-reported, lecanemab vs placebo: difference of [redacted] in favour of lecanemab. Health economic model: Increase QALY associated with the lecanemab arm.
Type of economic analysis that is submitted	Type of analysis: Cost-utility Type of model: Markov model
Data sources used to model the clinical effects	CSR-SB from Clarity AD used to derive transition probabilities (TP) during the model first 18 months for both lecanemab and SoC and used to estimate lecanemab treatment effect after 18 months.
Data sources used to model the health-related quality of life	Clarity AD EQ-5D-5L with Danish tariffs for MCI due to AD and Mild AD health states. Landeiro et al. 2020 is used to derive decrease in HRQoL from Mild AD to Moderate AD and to Moderate AD to Severe AD.
Life years gained	0.68 years
QALYs gained	[redacted] QALY
Incremental costs	DKK [redacted]
ICER (DKK/QALY)	[redacted] DKK/QALY
Uncertainty associated with the ICER estimate	Long-term treatment effect of lecanemab (time to worsening HR)
Number of eligible patients in Denmark	Incidence: [redacted] in year 5 Prevalence: [redacted] in year 5
Budget impact (in year 5)	DKK [redacted]

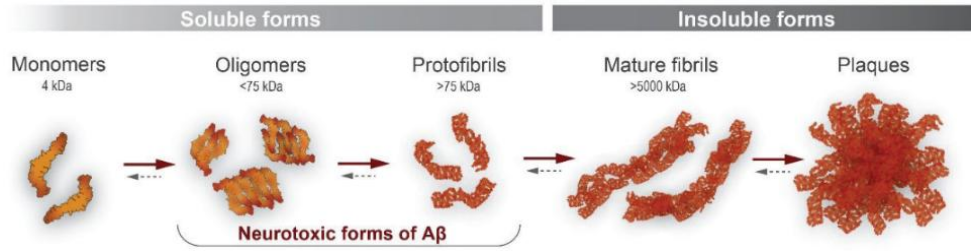
3. The patient population, intervention, choice of comparator(s) and relevant outcomes

3.1 The medical condition

3.1.1 Pathophysiology

AD is a fatal, neurodegenerative disease characterised by the deposition of extracellular Aβ plaques composed of aggregated Aβ peptides, and intracellular neurofibrillary tangles (NFT) composed of tau proteins. The accumulation of Aβ plaques and NFTs begins 15 – 20 years before any clinical manifestations of AD are detected. Aβ proteins aggregate through various forms of increasing sizes, including monomers, oligomers, protofibrils, fibrils, and eventually Aβ plaques (Figure 1) (4-8).

Figure 1 Amyloid plaque formation

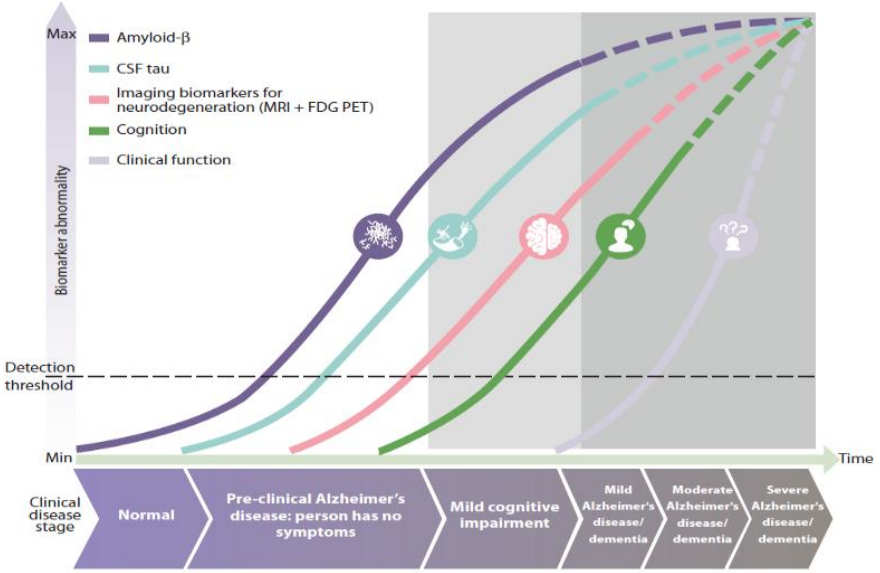


Source: Lannfelt, L. (2023) (9)
Abbreviations: kDa = Kilodalton

The buildup of Aβ starts a harmful chain reaction in AD, known as the amyloid cascade, 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 (5, 10-12). There is growing evidence to suggest that soluble Aβ protofibrils and oligomers are the most neurotoxic of all Aβ species (5, 10-15).

Aβ protofibrils have been shown to induce cell death, disturb healthy synapse activity, and impair important neurological functions, such as memory formation (5, 10-15). The pathological cascade of AD showing the change in Aβ and other key AD biomarkers over time is presented in Figure 2. The accumulation of brain Aβ can be detected first as decreasing levels of the soluble Aβ42 protein in cerebrospinal fluid (CSF) and plasma. As brain Aβ plaque levels increase, it can be detected with amyloid positron emission tomography (PET) imaging.

Figure 2 Model of AD pathological cascade



Source: Hampel et al., 2022 (16)
Abbreviations: Amyloid-β = Amyloid beta; CSF = Cerebrospinal fluid; FDG = Fluorodeoxyglucose; MRI = Magnetic resonance imagining; PET = Positron emission tomography

Aβ induces tau hyperphosphorylation and accumulation, which is detected as increased levels of phosphorylated tau (p-tau) proteins in the CSF and plasma as well as on tau PET. These molecular changes lead to neuronal degeneration, resulting in the disruption of synaptic function and integrity, and the release of synaptic proteins, such as neurogranin to the CSF. As neuronal degeneration proceeds, pieces of neuronal cytoskeleton (t-tau, neurofilament light chain [NfL]) can be observed in the CSF and plasma. Finally, neuronal

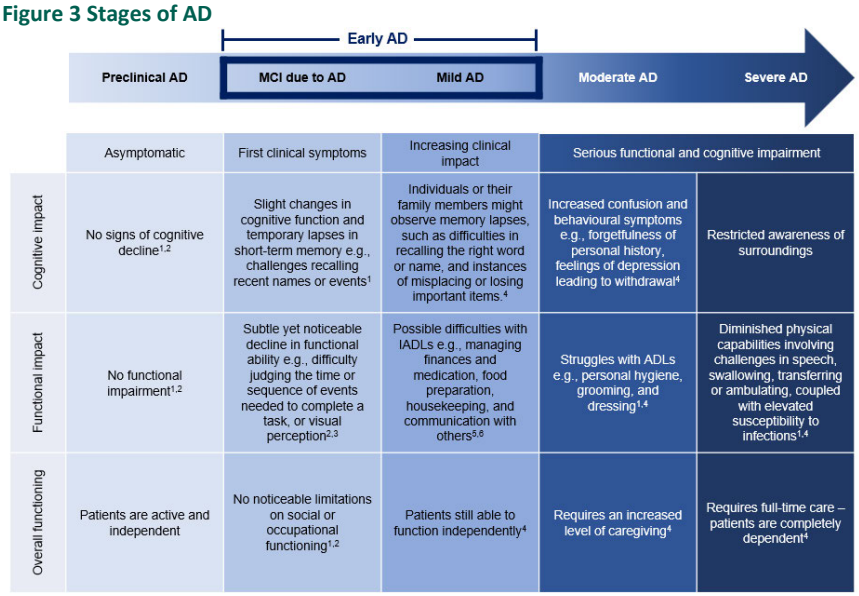
degeneration also becomes evident in structural (MRI) and functional (FDG PET) brain imaging, starting in the medial temporal lobe. In many cases, by the time AD is diagnosed, significant and irreversible brain damage has already occurred (17). This underscores the critical importance of early diagnosis and the need for timely intervention.

The amyloid cascade suggests that aggregation of Aβ is the initial trigger for the series of events that ultimately lead to AD. Therefore, targeting toxic Aβ species could inhibit the 'trigger' leading to the pathology seen in AD. The fundamental role of Aβ in the development of AD has been established by a number of studies in genetic syndromes affecting the amyloid pathway where overproduction of Aβ or reduced Aβ clearance are associated with the development of AD (18, 19). Late-onset (non-dominant or 'sporadic') AD is the most common form of AD, and typically occurs after the age of 60 (20). This form of AD is associated with the Apolipoprotein E (ApoE) gene, with the biggest genetic risk factor for late-onset AD being the presence of at least one ApoE ε4 allele with homozygosity presenting the highest risk for earlier onset (5, 10-15).

3.1.2 Clinical presentation/staging

AD progresses through several stages: preclinical, early AD (MCI due to AD and mild AD), and late-stage AD (moderate and severe AD) (21-26) (Figure 3). Preclinical AD represents the presence of AD pathological hallmarks including Aβ deposition and tau tangle formation, but an absence of clinical symptoms (22, 23). Thereafter, symptoms of typical AD begin in MCI due to AD with subtle changes in cognition and impairment in short-term memory, which gives rise to problems with planning, following instructions and making decisions, but still with the ability to keep up daily functioning.

Figure 3 Stages of AD



Source: 1: Alzheimer's Association 2018 (27); 2: Jack et al., 2018 (23); 3: Alzheimer's Association 2020 (28); 4: Alzheimer's Association 2020 (29); 5: Marshall et al., 2015 (30); 6: Kernisan et al., 2019 (31)
Abbreviations: AD = Alzheimer's disease; ADL = Activities of daily living; IADL = Instrumental activities of daily living; MCI = Mild cognitive impairment

As patients progress to mild AD, elements of cognition that decline include attention and concentration, language, visuospatial ability, executive function, fluency, and verbal IQ (32, 33). According to National Institute on Aging-Alzheimer's Association (NIA-AA) criteria, when the cognitive impairment is sufficiently great, such as interference with daily

function, the patient has progressed to the mild stage and is diagnosed with AD dementia (34).

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 (ADL) (35). Patients experience memory loss, delusions, confusion, and difficulty expressing thoughts, contributing to personality and behavioural changes such as frustration, suspicion, and anger. Patients with moderate AD also experience difficulty controlling their bladder and bowels, and show an increased tendency to wander and become lost, requiring a greater level of dependence on a caregiver (35). Severe AD is marked by severe cognitive impairment and an inability to perform basic daily functions, leading to complete dependence on caregivers. 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, 25, 35). 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 (21, 25, 35). As AD is a terminal disease, AD does eventually lead to the death of these patients.

3.1.2.1 Biological staging: AT(N) system

AD is a continuum, characterised by the accumulation of amyloid, hyperphosphorylation of tau, and neurodegeneration. Biological staging has been incorporated in the NIA-AA research framework through an AT(N) biomarker profile with 'A' denoting amyloid, 'T' aggregated tau, and 'N' neurodegeneration (23). The buildup of Aβ triggers the amyloid cascade, followed by the formation of tau tangles (i.e., neurofibrillary tangles, NFT), marking disease progression, leading to synaptic dysfunction, synapse loss, and neurodegeneration (5, 10-12).

3.1.3 Patient prognosis

Current available therapies for AD, which consist of symptomatic treatment, provide only temporary and symptomatic relief, and do not treat the underlying cause of AD, nor cure or halt the progression of the disease (36, 37). In addition, there is no approved medical treatment for subjects with MCI due to AD. In Denmark, dementia (AD aetiology most common) is the fourth most common cause of death (38), which has led to approximately 4 400 excess deaths annually among patients with dementia (38).

3.1.4 Health-related quality of life

AD is a disease with a severe impact on the QoL of patients and caregivers. There is a significant unmet medical need for a treatment that can slow the progression of AD and delay the time until the patient reaches the debilitating stages of the disease characterized by full time care, surveillance, institutionalization, and death.

Clinically-diagnosed MCI is associated with lower QoL, increased psychiatric burden (e.g., depression), and reduced social activity, which can worsen as the disease advances (39, 40). Patients' QoL decreases significantly as the patient leaves the mild stage of AD, as AD invariably leads to a broad spectrum of negative consequences of cognitive and functional impairment and behavioural and mental challenges and, ultimately, a complete inability to lead an independent life.

The burden of caregiving is detrimental to mental and physical wellbeing, leaving carers in poorer health (41). Those caring for spouses have 2.5 times higher odds of suffering with depression, than those who are not caregivers of spouses (41). Often, caregivers must rely on a support system and coping strategies in order to mediate their increasing levels of stress (42). The stress of providing care to patients with dementia adversely impacts caregiver physical, mental, and social health. Caregivers have increased susceptibility to other health complications, such as a higher risk of cardiovascular disease and impaired kidney function and depression (41).

The unmet need is heightened for patients with MCI due to AD and mild AD who have the potential to remain in less severe stages of disease for longer. Delaying disease progression would prolong the time patients are able to function independently, prolong time spent with higher QoL, delay increased burden on their caregivers, and delay the risk of further irreversible decline (43).

3.2 Patient population

The diagnosis of AD requires a multidisciplinary team of specialists (i.e., general practitioners, occupational therapists, radiologists, psychiatrists, neurologists, and geriatricians) who use a variety of tools when assessing patients with suspected AD including clinical examination, imaging, and biological staging (biomarkers).

Patient diagnosis

Patients with suspected AD will undergo a basic assessment in a primary care setting, where patients initially start with structured interviews to determine their everyday functional and activity levels, cognitive ability, and psychological symptoms (44). Ideally, these interviews should be done with a relative (or other persons with whom the person with suspected AD has a close relationship with) to determine how the patient's cognitive or functional ability has changed over time and the effect of AD on daily life (44). In Denmark, the Mini-Mental State Exam (MMSE) is often used, additional tests also include the Montreal Cognitive Assessment (MoCA), Brief Assessment of Impaired Cognition (BASIC) or Addenbrooke's Cognitive Examination-III (ACE-III) (44). Blood tests may also be conducted to rule out any underlying conditions which may be causing cognitive impairment (44).

Computed tomography (CT) scans or MRIs are routinely offered to patients with suspected AD to determine if there are underlying causes other than AD that may be causing cognitive impairment (44). PET imaging for Aβ and tau are used at highly specialised centres (44). Without biomarkers, a diagnosis of AD can, at best, be made with 70% certainty. With biomarkers, this certainty increases to over 90% (45).

In Denmark, CSF biomarkers are used to detect Aβ1-42, total-tau, p-tau or the ratio between Aβ42/p-tau to confirm AD (44).

At present, ApoE testing is only used in research settings and not in standard clinical practice in Denmark. However, the test is commercially available, affordable, and could easily be implemented for patients who are candidates for anti-Aβ treatments.

Incidence and prevalence of early AD

According to the *Dansk Klinisk Kvalitetsdatabase for Demens* (DanDem) 2023 annual report, 2929 patients were diagnosed with AD in 2023 (3652 reported in 2022), and for all cause dementia the distribution of MCI due to AD and mild dementia is 20 and 33% respectively (46).

Table 1 Incidence and prevalence in the past 5 years

Year	2019	2020	2021	2022	2023
Incidence of diagnosed AD in Denmark	3 291*	3 291*	3 291*	3 652	2 929
Incidence of early AD in Denmark#	1 744	1 744	1 744	1 936	1 552
Prevalence all cause dementia in Denmark^	97 300	97 300#	97 300#	97 300#	97 300#
Global prevalence	57.4 million people with dementia (47)				

*Estimate provided based on an average of the 2022 and 2023 number of patients diagnosed with AD reported in DanDem report, as previous reports are not available.
Estimate provided based on distribution of MCI due to AD (*Kognitiv svækket - ikke dement*) and mild dementia (*Demens i let grad*) patients from DanDem; (20%+33%) x AD incidence
^Limited information available for prevalence of AD, all cause dementia number is taken from *Nationalt videnscenter for demens* based on dementia diagnosis (48)
Abbreviations: AD = Alzheimer's disease

The number of AD patients who are candidates for lecanemab is limited by several factors. Treatment with lecanemab will be handled by specialised memory clinics, and only patients referred to and diagnosed at a memory clinic are potential candidates. Currently, the median waiting time for a first visit at a memory clinic is 77 days (46). AD diagnosis must also be confirmed by Aβ biomarker detection by CSF or by an amyloid PET scan. Additionally, patients are also required to undergo an MRI scan and present an acceptable baseline safety scan. The eligible patient group is further limited by the indication of lecanemab to early AD patients who are ApoE ε4 non-carriers or heterozygotes. Eligibility will also be limited by comorbidity, concomitant treatment, individual risk-benefit assessment, and personal circumstances and preferences.

In [redacted] the potential number of incident eligible patients is estimated using data from DanDem (46). Of those who are diagnosed with AD, the share who have had the Aβ biomarker confirmed by CSF or PET is estimated by applying the percentage of all examined patients at the memory clinic having a biomarker confirmed diagnosis. This assumption was made as the AD-specific share was not available in the DanDem report. Similarly, the share of patients with a clinical diagnosis of all type MCI or mild dementia was applied to arrive at the number of biomarker-confirmed AD patients with MCI due to AD and mild AD, since the share of patients with a clinical diagnosis of AD was not reported in DanDem.

There was no data for AD patients with an MRI. Therefore, taking contraindications for MRI into account, a share of [redacted] was estimated and applied. Of these patients with a biomarker confirmed diagnosis of early AD with an MRI, 15% were excluded as being ApoE ε4 homozygous according to the indication, based on a systematic review of the prevalence of ApoE ε4 homozygotes in the AD population (49) and the distribution in Clarity AD (50). In the final step, [redacted] estimated by a Danish AD expert (51)) of the remaining patients were estimated to meet eligibility criteria. This [redacted] accounted for patients not being eligible to receive lecanemab due to co-morbidities, MRI findings,

anticoagulant treatment, and other potential exclusion criteria. Finally, to account for the potential uncertainties in the assumptions, the estimates and final patient number in Figure 4 were validated by a Danish AD expert (51).

Abbreviations: AD = Alzheimer's disease; CSF = cerebrospinal fluid; MCI = Mild cognitive impairment; MRI = Magnetic resonance imaging

Table 2 reports the estimated number of incident early AD patients in Denmark over the next five years who are eligible for treatment with lecanemab.

Table 2 Estimated number of incident patients eligible for treatment

Year	Year 1	Year 2	Year 3	Year 4	Year 5
Number of incident patients in Denmark who are eligible for treatment in the coming years					

3.3 Current treatment options

The treatment guideline from Sundhedsstyrelsen, *National klinisk retningslinje for udredning og behandling af demens* (updated 2013) informs current treatment options in Denmark (2). However, the guideline is currently being updated and is considered obsolete, as per Sundhedsstyrelsen (2).

At present, pharmacological treatment is comprised of symptomatic treatment: three acetylcholinesterase inhibitors (AChEIs; donepezil, galantamine, rivastigmine) and one N-methyl-D-aspartate (NMDA; memantine) receptor antagonist (2). These treatments provide temporary reduction in symptoms, but do not treat the underlying cause of AD, nor delay disease progression (2).

There are currently no pharmacological treatment options recommended for patients with MCI due to AD (2). AChEIs are recommended in patients with mild and moderate AD while memantine is recommended in moderate to severe AD. Combination therapy with one AChEI and memantine is not routinely recommended, as there is not enough evidence to support the efficacy of the combination treatment in AD patients compared to AChEIs and memantine alone (2).

3.4 The intervention

Overview of intervention	
Therapeutic indication relevant for the assessment	Lecanemab is indicated for the treatment of adult patients with a clinical diagnosis of mild cognitive impairment and mild dementia due to Alzheimer's disease (Early Alzheimer's

	disease) who are apolipoprotein E ε4 (ApoE ε4) non-carriers or heterozygotes with confirmed amyloid pathology (1).
ATMP	N/A
Method of administration	IV infusion
Dosing	10 mg/kg biweekly. [redacted] (see Appendix N)
Dosing in the health economic model (including relative dose intensity)	10 mg/kg biweekly RDI = 95.26% for Core Study and 93.40% for OLE Study
Should the medicine be administered with other medicines?	No
Treatment duration / criteria for end of treatment	Treatment with lecanemab should be discontinued once the patient progresses to moderate AD (1).
Necessary monitoring, both during administration and during the treatment period	Recent (within 6 months) baseline brain MRI must be obtained prior to initiating treatment with lecanemab to evaluate for pre-existing ARIA. Obtain an MRI prior to the 5th, 7th and 14th infusions. If a patient experiences symptoms suggestive of ARIA at any time during treatment, clinical evaluation should be performed including an MRI (1).
Need for diagnostics or other tests (e.g. companion diagnostics). How are these included in the model?	Prior to initiating treatment, the presence of ApoE ε4 genotype and Aβ pathology should be confirmed by appropriate diagnostic tests (1).
Package size(s)	Leqembi® (lecanemab) 100 mg/mL concentrate for solution for infusion. Available as (52): one vial of 2 mL; 200 mg of lecanemab one vial of 5 mL; 500 mg of lecanemab

Abbreviations: AD = Alzheimer's disease; ARIA = Amyloid related imaging abnormalities; EMA = European Medicines Agency; IV = intravenous; MCI = mild cognitive impairment; MRI = magnetic resonance imaging; OLE = open-label extension

3.4.1 Description of ATMP

N/A

3.4.2 The intervention in relation to Danish clinical practice

Lecanemab is expected to be offered to adult patients with a clinical diagnosis of early AD (MCI due to AD or mild AD) who are ApoE ε4 non-carriers or heterozygotes with confirmed amyloid pathology. For patients with MCI due to AD, lecanemab will be the only treatment option as symptomatic medications are only indicated for patients who have progressed to dementia due to AD.

In contrast to existing symptomatic treatments (i.e., AChEIs and memantine), lecanemab slows disease progression. However, symptomatic treatments will continue to be offered to patients with mild AD, as symptomatic treatments can be used in combination with lecanemab, where required. Lecanemab is not expected to displace these treatments.

In Clarity AD, patients received AChEI and memantine at both the MCI due to AD and mild AD stages, and is expected to be representative of the Danish clinical practice.

3.4.3 Mechanism of action

Lecanemab is a humanised monoclonal antibody (IgG1) that binds to toxic Aβ peptides, marking them for clearance via the immune system. Lecanemab demonstrates a unique dual mechanism of action that reduces the amount of neurotoxic protofibrils in the AD brain while clearing amyloid plaques at the same time. Specifically, it binds with the highest affinity to soluble, neurotoxic Aβ protofibrils and oligomers, whilst maintaining binding activity to insoluble fibrils and plaques, resulting in Aβ plaque clearance as demonstrated in preclinical studies (Figure 2) (53-55). Once bound, lecanemab has been shown to internalise Aβ protofibrils into immune cells and mediate macrophage-induced plaque clearance in AD brain sections (56). The clearance of neurotoxic Aβ, in return, slows down the spread of tau that occurs downstream of Aβ accumulation and deposition.

In Clarity AD, lecanemab demonstrated a clear effect on amyloid and tau pathology by reducing amyloid burden(measured by PET and in CSF) and, abnormal levels of p-tau seen in CSF and blood, as well as reducing the amount of tau depositions seen on tau PET. Lecanemab is a low-risk molecule for immunogenicity based on ADA profile and minimal impact of ADA on pharmacokinetics, pharmacodynamics, efficacy, and safety (57).

Cerebral amyloid angiopathy (CAA), or the deposition of Aβ in vessel walls, is a phenomenon observed in cognitively normal elderly, but also frequently in patients with AD. In AD, CAA is tightly linked to the development of “amyloid-related imaging abnormalities (ARIA)”, a frequently occurring side-effect of anti-Aβ immunotherapy defined by neuroimaging. Unlike the plaques in the brain parenchyma, which consist mainly of Aβ42, these vascular plaques consist mainly of Aβ40. Importantly. Lecanemab has been designed to demonstrate selectivity towards Aβ42 and with low binding to Aβ40 to minimize the effect on vascular plaques and the risk of ARIA (55).

3.5 Choice of comparator(s)

As only symptomatic treatments are available to early AD patients, placebo plus SoC is considered as the relevant comparator for this submission.

3.6 Cost-effectiveness of the comparator(s)

N/A

3.7 Relevant efficacy outcomes

3.7.1 Definition of efficacy outcomes included in the application

Table 3 Efficacy outcome measures relevant for the application

Outcome measure	Time point*	Definition	How was the measure investigated/method of data collection
CDR-SB (58)	18 months for Core Study, 36 months for OLE Study	Primary outcome. Change from baseline in the CDR-SB. Used to stage the severity of cognitive and functional impairment via interview, discerning changes over time (59).	Interview is administered by a qualified clinical professional, reported by the patient and study partner (60).

ADAS-Cog14 (61, 62)	18 months for Core Study, 36 months for OLE Study	Secondary outcome. Change from baseline in ADAS-Cog14. 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 (62).	Score is administered by clinician and includes both patient-completed tests and assessments observed by the clinician (60).
ADCS MCI-ADL (63)	18 months for Core Study, 36 months for OLE Study	Secondary outcome. Change from baseline in ADCS MCI-ADL. 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.	Score is administered by clinician, caregiver-reported (60).
Time to worsening of CDR-SB	18 months for Core Study.	Exploratory outcome. Time to worsening of CDR-SB. The worsening of CDR-SB was defined as the CDR-SB score increasing from MCI due to AD at baseline to a worse AD severity level (mild, moderate, or severe AD), or mild AD at baseline to a worse AD severity level (moderate or severe AD) based on the first worsening where a worsening is observed in 2 consecutive visits.	Interview is administered by a qualified clinical professional, reported by the patient and study partner (60).

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 Scale for Mild Cognitive Impairment; CDR-SB = Clinical Dementia Rating-sum of boxes; OLE = open label extension.

Validity of outcomes

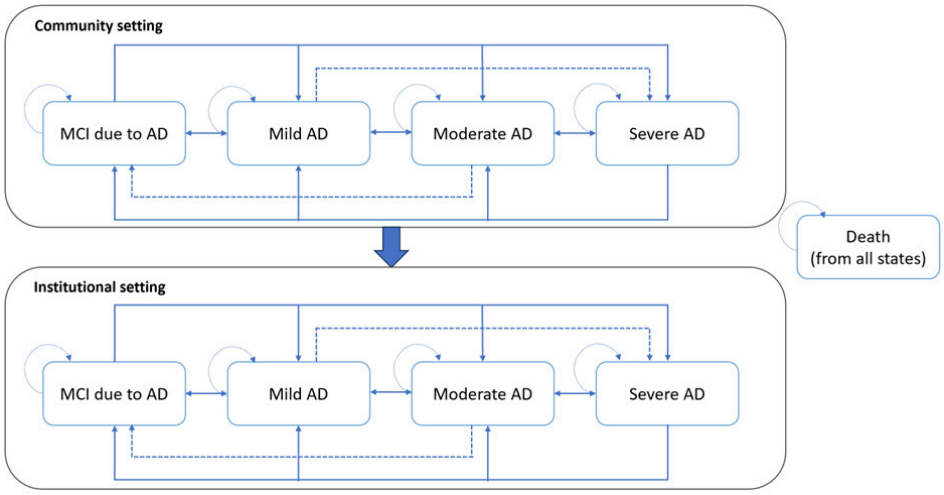
CDR-SB, ADAS-Cog14, and ADCS MCI-ADL are well established outcome measures used in clinical trials of AD and have been accepted by EMA and FDA regulators for AD clinical trials. A detailed description of the CDR-SB criteria and other outcomes is provided in Table 110 and Table 111 in Appendix K.1.

4. Health economic analysis

4.1 Model structure

A Markov model was developed to perform the cost-effectiveness analysis. Markov models are the most commonly used approach among previously published cost-effectiveness studies in AD (64). The model is comprised of nine health states (Figure 5), representing disease severity (MCI due to AD, Mild, Moderate, and Severe AD) replicated in the community and institution setting, and death.

Figure 5 Model structure



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

To align with the primary endpoint of Clarity AD (60), CDR-SB was used to define health states in the base case. CDR-SB was preferred over global CDR as it provides increased precision in tracking changes between stages, with the score ranging from 0 to 18 (vs 0-3 for global CDR). This translates to a more precise interpretation of progression, especially in the early stages of the disease, as CDR-SB can discriminate between patients with very early AD and those with MCI (59). In addition, there was a lack of natural history data based on Global CDR. The CDR-SB thresholds defining disease severity were based on the categories reported by O'Bryant (59) as shown in Table 4.

Table 4 Health states definition

Endpoint	MCI due to AD	Mild AD	Moderate AD	Severe AD
CDR-SB (base case)	0.5–4.0	4.5–9.0	9.5–15.5	16.0–18.0
Global CDR	0.5	1.0	2.0	3.0

Source: O'Bryant et al., 2008 (59)
Abbreviations: AD= Alzheimer's disease; CDR= clinical dementia rating; CDR-SB= clinical dementia rating – sum of boxes; MCI= mild cognitive impairment

Patients enter the model in either the 'MCI due to AD' or 'Mild AD' health state. If not stated otherwise, the data from Clarity AD leveraged in the model is derived specifically from the ApoE ε4 non-carrier and heterozygous population, in alignment with the lecanemab EMA indication.

The distribution of patients across these health states in the first model cycle represents the CDR-SB distribution at baseline in the Clarity AD intent to treat (ITT) full analysis set+ (FAS+) ApoE ε4 non-carrier and heterozygous population. It is assumed that all patients enter the model in the community setting, as per Clarity AD. At each model cycle, patients can either progress, move to a less severe state, get institutionalised, or die.

Disease progression was estimated using transition probabilities (TPs) derived from the Clarity AD study for the first 18 months of the time horizon, which corresponds to the randomised phase of the trial (60). As data for Moderate AD and Severe AD were immature, natural history data from the literature was leveraged to estimate disease

progression after 18 months. Backward transitions were permitted as observed in Clarity AD and in literature (65).

The risk of institutionalisation was not reported in Clarity AD and was therefore sourced from literature. Published evidence indicated that once patients are institutionalised, they are unlikely to return to a community setting and therefore transitions from institution to community were not permitted in the model (66, 67). The AD-specific risk of mortality was also derived from the literature, as less than 1% of patients died in either arm of Clarity AD by the end of the Core Study.

In addition to health state transitions, patients are subjected to the risk of lecanemab discontinuation and adverse events. These risks are modelled 'within state' and are not considered structural components of the model. Discontinuation of lecanemab was assumed to occur due to all-cause discontinuation as observed in Clarity AD. In addition, patients were assumed to stop treatment after transition to the Moderate or Severe AD health state and when institutionalised. Adverse events (AEs) modelled included ARIA (ARIA-E and isolated ARIA-H) and infusion-related reactions.

4.2 Model features

The key model features are described in Table 5.

Table 5 Features of the economic model

Model features	Description	Justification
Patient population	Patients with early AD (MCI due to AD and Mild AD)	As per Clarity AD ITT FAS+ ApoE ε4 non-carriers and heterozygous population
Perspective	Limited societal perspective	According to DMC guidelines
Time horizon	Lifetime (30 years)	All patients transitioned to the death health state by the end of the time horizon
Cycle length	1 month	Accommodates biweekly lecanemab administrations and recurrent annual costs, with minimum data manipulation
Half-cycle correction	Yes	-
Discount rate	3.5 %	The DMC applies a discount rate of 3.5% for all years
Intervention	Lecanemab biweekly 10 mg/kg IV infusions	As per Clarity AD (68). [redacted] (Appendix N)
Comparator(s)	SoC	According to national treatment guideline and confirmed by clinical experts within the Nordics advisory board (69).
Outcomes	AD progression by CDR-SB, institutionalisation, and mortality	Progression per primary outcome of Clarity AD, plus institutionalisation and mortality as key events for AD patients

Abbreviations: AD = Alzheimer's disease; DMC = Danish medicines council; FAS+ = full analysis set; ITT = intent to treat; MCI = Mild cognitive impairment; SoC = standard of care

5. Overview of literature

5.1 Literature used for the clinical assessment

A clinical systematic literature review (SLR) was conducted in May 2024, the full details of which are provided in Appendix H. In summary, 64 publications were identified, which included 16 unique trials. From these, Clarity AD (70) was considered most appropriate to inform the head-to-head comparative efficacy and safety evidence of lecanemab vs placebo for MCI due to AD and mild AD patients.

Table 6 Relevant literature included in the assessment of efficacy and safety

Reference (Full citation incl. reference number)*	Trial name	NCT identifier	Dates of study (Start and expected completion date, data cut-off and expected data cut-offs)	Used in comparison of*
van Dyck CH, Swanson CJ, Aisen P, Bateman RJ, Chen C, Gee M, Kanekiyo M, Li D, Reyderman L, Cohen S, Froelich L, Katayama S, Sabbagh M, Vellas B, Watson D, Dhadda S, Irizarry M, Kramer LD, Iwatsubo T. Lecanemab in Early Alzheimer's Disease. N Engl J Med. 2023 Jan 5;388(1):9-21. doi: 10.1056/NEJMoa2212948. Epub 2022 Nov 29. PMID: 36449413. (70) Cohen S, van Dyck CH, Gee M, Doherty T, Kanekiyo M, Dhadda S, Li D, Hersch S, Irizarry M, Kramer LD. Lecanemab Clarity AD: Quality-of-Life Results from a Randomized, Double-Blind Phase 3 Trial in Early Alzheimer's Disease. J Prev Alzheimers Dis. 2023;10(4):771-777. doi: 10.14283/jpad.2023.123. PMID: 37874099. (71) 2023 Clarity AD CTAD presentation (72) Clinical Study Report, Core Study [Data on file] (68) Interim Clinical Study Report, OLE Study [Data on file] (73)	Clarity AD	NCT03887455	Start: 27/03/2019 Completion: 15/09/2027 Data cut-off: 13/09/2022 (Core Study, completed) 30/11/2023 (OLE Study, ongoing)	Lecanemab vs. placebo for MCI due to AD and Mild AD patients

5.2 Literature used for the assessment of health-related quality of life

An SLR was conducted to identify the health state utility data associated with all stages of AD (including MCI due to AD and mild-moderate-severe dementia due to AD), described in in Appendix I.

Farina et al. 2020 (74), identified through the SLR, explored the relationship between disease severity (by MMSE) and QoL of people with dementia and their family carers using EQ-5D-3L conducting a series of multiple regression analyses. Landeiro et al. 2020 (75), identified through a hand search, conducted an SLR and a meta-analysis to summarise their reported HRQoL levels at each stage of the disease and by type of respondent.

Table 7 Relevant literature included for (documentation of) health-related quality of life

Reference (Full citation incl. reference number)	Health state/Disutility	Reference to where in the application the data is described/applied
Landeiro, F., Mughal, S., Walsh, K., Nye, E., Morton, J., Williams, H., ... & ROADMAP consortium. (2020). Health-related quality of life in people with predementia Alzheimer's disease, mild cognitive impairment or dementia measured with preference-based instruments: a systematic literature review. Alzheimer's research & therapy, 12, 1-14.(75)	Disutility applied to mild AD and moderate AD health state to derive the moderate AD and severe AD utility values, respectively.	Section 10.2.3
Farina, N., et al., Disease severity accounts for minimal variance of quality of life in people with dementia and their carers: analyses of cross-sectional data from the MODEM study. BMC geriatrics, 2020. 20: p. 1-13.(74)	Disutility for institutionalisation applied in moderate AD and severe AD and used in the scenario analysis applied to mild AD and moderate AD health state to derive the moderate AD and severe AD utility values, respectively.	Section 10.2.3
Boye KS, Matza LS, Walter KN, Van Brunt K, Palsgrove AC, Tynan A. Utilities and disutilities for attributes of injectable treatments for type 2 diabetes. Eur J Health Econ. 2011 Jun;12(3):219–30. (76)	Disutility of AE applied in scenario analysis as requested by DMC on May 20, 2025	Section 10.2.3
Meckley LM, Gudgeon JM, Anderson JL, Williams MS, Veenstra DL. A policy model to evaluate the benefits, risks and costs of warfarin	Disutility of AE applied in scenario analysis as requested by DMC on May 20, 2025	Section 10.2.3

Reference (Full citation incl. reference number)	Health state/Disutility	Reference to where in the application the data is described/applied
pharmacogenomic testing. Pharmacoeconomics. 2010;28(1):61–74. (77)		
Sullivan PW, Ghushchyan V. Preference-Based EQ-5D index scores for chronic conditions in the United States. Med Decis Making. 2006;26(4):410–20 (78)	Disutility of AE applied in scenario analysis as requested by DMC on May 20, 2025	Section 10.2.3

5.3 Literature used for inputs for the health economic model

The literature search conducted to identify the current evidence that describes economic evaluation studies in patients with MCI due to AD and AD is described in Appendix J. In Table 8, the literature used for input to the economic model is listed.

Table 8 Relevant literature used for input to the health economic model

Reference (Full citation incl. reference number)	Input/estimate	Method of identification	Reference to where in the application the data is described/applied
Potashman, M., et al., Estimating Progression Rates Across the Spectrum of Alzheimer's Disease for Amyloid-Positive Individuals Using National Alzheimer's Coordinating Center Data. Neurol Ther, 2021. 10(2): p. 941-953.2021 (65)	Natural history of the disease (CDR-SB)	TLR	Section 8.2.1
Crowell V, Reyes A, Zhou SQ, Vassilaki M, Gsteiger S, Gustavsson A. Disease severity and mortality in Alzheimer's disease: an analysis using the U.S. National Alzheimer's Coordinating Center Uniform Data Set. BMC Neurol. 2023;23(1):302.	Mortality due to AD based on AD severity	Hand search	Section 8.2.2

Reference (Full citation incl. reference number)	Input/estimate	Method of identification	Reference to where in the application the data is described/applied
Knapp M, Chua KC, Broadbent M, Chang CK, Fernandez JL, Milea D, et al. Predictors of care home and hospital admissions and their costs for older people with Alzheimer's disease: findings from a large London case register. BMJ Open. 2016;6(11):e013591	Institutionalisation risk based on AD severity	Hand search	Section 8.2.3
Belger, Mark, et al. "Determinants of time to institutionalisation and related healthcare and societal costs in a community-based cohort of patients with Alzheimer's disease dementia." The European Journal of Health Economics 20 (2019): 343-355.	Used as scenario analysis for institutionalisation risk based on AD severity	Hand search	Section 8.2.3
Aye et al., Costs of Care in Relation to Alzheimer's Disease Severity in Sweden: A National Registry-Based Cohort Study. PharmacoEconomics, 2024: p. 1-1 (79)	Health state costs	Hand search	Direct medical and non-medical costs, Section 11.4
Landeiro, F., Mughal, S., Walsh, K., Nye, E., Morton, J., Williams, H., ... & ROADMAP consortium. (2020). Health-related quality of life in people with predementia Alzheimer's disease, mild cognitive impairment or dementia measured with preference-based instruments: a systematic literature review. Alzheimer's research & therapy, 12, 1-14.(75)	Disutility applied to Mild AD and Moderate AD health state to derive the Moderate AD and Severe AD utility values, respectively.	Hand search	Section 10.2.3
Farina, N., et al., Disease severity accounts for minimal variance of quality of life in people with dementia and their carers: analyses of cross-sectional data from the MODEM study. BMC geriatrics, 2020. 20: p. 1-13.(74)	Disutility for institutionalisation applied in Moderate AD and Severe AD	SLR (Appendix I)	Section 10.2.3
Cummings, J., et al. "Lecanemab: appropriate use recommendations." The journal of prevention of Alzheimer's disease 10.3 (2023): 362-377. (80)	Appropriate management of ARIA events and IRR. Specifically, MRI and GP resource use; antihistamines, paracetamol, dexamethasone and methylprednisolone treatments dosing schedule	Hand search	Section 0

Reference (Full citation incl. reference number)	Input/estimate	Method of identification	Reference to where in the application the data is described/applied
Boye KS, Matza LS, Walter KN, Van Brunt K, Palsgrove AC, Tynan A. Utilities and disutilities for attributes of injectable treatments for type 2 diabetes. Eur J Health Econ. 2011 Jun;12(3):219–30. (76)	Disutility of AE applied in scenario analysis as requested by DMC on May 20, 2025	Hand search	Section 10.2.3
Meckley LM, Gudgeon JM, Anderson JL, Williams MS, Veenstra DL. A policy model to evaluate the benefits, risks and costs of warfarin pharmacogenomic testing. Pharmacoeconomics. 2010;28(1):61–74. (77)	Disutility of AE applied in scenario analysis as requested by DMC on May 20, 2025	Hand search	Section 10.2.3
Sullivan PW, Ghushchyan V. Preference-Based EQ-5D index scores for chronic conditions in the United States. Med Decis Making. 2006;26(4):410–20 (78)	Disutility of AE applied in scenario analysis as requested by DMC on May 20, 2025	Hand search	Section 10.2.3

6. Efficacy

6.1 Efficacy of lecanemab vs placebo for adult patients with MCI due to AD and Mild AD who are ApoE4 non-carriers or heterozygotes

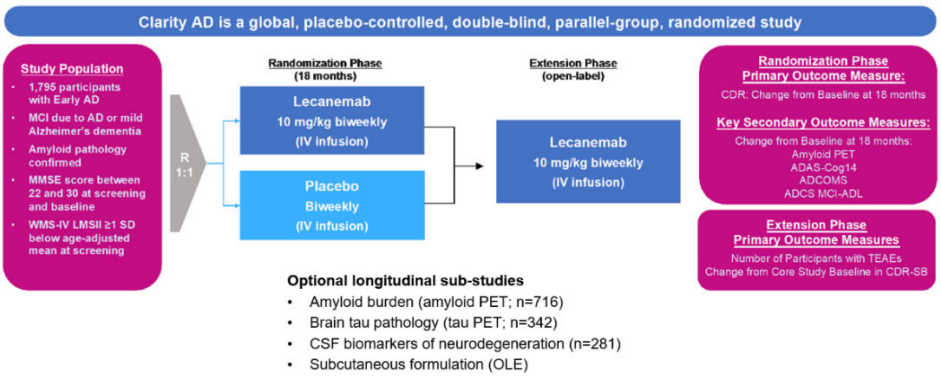
6.1.1 Relevant studies

Clarity AD Core Study (NCT03887455) is a randomised, double-blind, parallel-group, placebo-controlled, multicentre phase 3 clinical trial that evaluates the efficacy and safety of biweekly IV lecanemab 10 mg/kg in patients with early AD (MCI due to AD and mild AD) with confirmed amyloid pathology over 18 months (50). The Clarity AD Core Study provides evidence on the effect of lecanemab across all key outcomes of the trial such as CDR-SB, ADAS-Cog14, and ADCS MCI-ADL, among others. The study consisted of a pre-randomisation phase (screening period and baseline period, up to 150 days), an 18-month Core Study, followed by an OLE study of up to 48 months (50, 81).

Figure 6 presents the Clarity AD study design. Three longitudinal substudies were conducted during Clarity AD through amyloid PET, CSF biomarker assessments, and tau PET, to assess engagement and the effect on downstream processes in the amyloid cascade, including the effect on tau pathology, inflammation and synapse biomarkers (50, 81). Both arms continued to receive symptomatic treatment for AD if they were on a stable dose at least 12 weeks prior to baseline.

Clarity AD OLE (NCT03887455) is an open-label extension of the Clarity AD Core Study. Any subject who completed Visit 42 (Week 79) of the Core Study had the option to participate in the OLE study, if the OLE study inclusion and exclusion criteria were met. Subjects who participated in the Core Study and completed their final Core Visit (Visit 42) continued seamlessly into the OLE study. There were 2 groups of lecanemab-naïve subjects in the OLE study: Core placebo subjects and subjects who did not participate in the Core Study (*de novo* subjects) (82). The OLE study will last for up to 48 months (4 years) (82).

Figure 6 Clarity AD study design



Source: Eisai CTAD presentation (2023) (72)
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 Scale for Mild Cognitive Impairment; ApoE ε4 = apolipoprotein E4; CDR-SB = Clinical Dementia Rating-sum of boxes; CSF = cerebrospinal fluid; IV = intravenous; MCI = mild cognitive impairment; MMSE = Mini-Mental State Exam; OLE = open-label extension; PET = positron emission tomography; SD = standard deviation; TEAEs = treatment emergent adverse events; WMS-IV LMSII = Wechsler Memory Scale IV-Logical Memory (subscale) II.The Randomization phase in this graphic represents the Core Study of Clarity AD.

In the Core Study, a total of 1521 ApoE ε4 non-carrier and heterozygous patients were randomised, with 757 assigned to lecanemab and 764 assigned to placebo (83). More than 80% of randomised patients completed the Core Study (lecanemab group: 81.6%

[618/757], placebo group: 83.8% [640/764]). Of the patients who discontinued the study, reasons for discontinuation were similar between lecanemab and placebo, with the most common reasons being withdrawal of consent and adverse events (AEs) (Table 9) (83).

Table 9 Study Discontinuations; Clarity AD Core Study (Randomised Set), ApoE ε4 Non-carriers and Heterozygotes

Characteristic	Lecanemab	Placebo	Total
Patients randomised and assigned, n	[redacted]	[redacted]	[redacted]
Patients completing study, n (%)	[redacted]	[redacted]	[redacted]
Patients discontinuing study, n (%)	[redacted]	[redacted]	[redacted]
Reasons for Discontinuation			
Withdrew consent, n (%)	[redacted]	[redacted]	[redacted]
AE, n (%)	[redacted]	[redacted]	[redacted]
Subject choice, n (%)	[redacted]	[redacted]	[redacted]
Lost to follow up, n (%)	[redacted]	[redacted]	[redacted]
Other, n (%)	[redacted]	[redacted]	[redacted]

Source: Eisai DOF (Table 14.1.1.3.1) (83)
Abbreviations: AD = Alzheimer's Disease; AE = adverse event

In the OLE Study, at 36 months (18 months of Core Study + 18 months of OLE), [redacted] ApoE ε4 non-carriers and heterozygous patients received study treatment, of which [redacted] patients had ongoing treatment, and [redacted] patients discontinued (Table 10)(84). The most common reasons for discontinuation were withdrawal of consent, subject choice, and AE (84).

Patients in OLE Study could transfer over to the subcutaneous (SC) substudy, should they fulfil the inclusion criteria at any timepoint after the 18-month Core Study. These patients were excluded from the ITT FAS+ analysis set: only patients who were on the IV lecanemab formulation were included. Thus, results may show an artificially higher attrition rate, since these patients are not accounted for in the subject disposition below and during the follow-up timepoints, when in fact, these patients have transferred into the SC substudy.

Table 10 Subject Disposition and Primary Reason for Discontinuation from Study Clarity AD OLE Phase (OLE Treated Set), ApoE ε4 Non-carriers and Heterozygotes

	Newly Treated Core Placebo	Core 10 mg/kg Biweekly	Total
Treated, n (%)	609 (100)	578 (100)	1187 (100)
Ongoing in study, n (%)	451 (74.1)	449 (77.7)	900 (75.8)
Transitioned to subcutaneous substudies*	154 (21.4)	156 (23.2)	310 (22.3)
Discontinued from study, n (%)	158 (25.9)	129 (22.3)	287 (24.2)
Reason for Discontinuation			
Adverse event[b], n (%)	39 (6.4)	19 (3.3)	58 (4.9)
Subject choice, n (%)	32 (5.3)	41 (7.1)	73 (6.1)
Lost to follow-up, n (%)	4 (0.7)	6 (1.0)	10 (0.8)
Withdrawal of consent, n (%)	57 (9.4)	37 (6.4)	94 (7.9)
Other, n (%)	26 (4.3)	26 (4.5)	52 (4.4)

Source: Eisai DOF (Table 14.1.1.3.1nh) (84); Eisai OLE CSR v5.0 (Table 1) (82)
Note: * based on the OLE Treated Set of the full population [redacted] ApoE ε4 carriers, non-carriers and heterozygotes)
Core 10 mg/kg biweekly subjects are those assigned to lecanemab (10 mg/kg biweekly) in Core Study, and newly treated Core placebo subjects are those assigned to placebo in Core Study. Percentages are based on the number

of subjects treated in OLE Phase in the relevant treatment group. Data collected after subjects switch to/start SC dose are not included. a: As reported on the Disposition – OLE Phase CRF. b: Corresponding adverse event(s) leading to discontinuation from the study were reported on the Adverse Event CRF.
Abbreviations: ApoE ε4 = Apolipoprotein E4; CRF = Case report form, OLE = Open-label extension.

Table 11 Overview of study design for studies included in the comparison

Trial name, NCT-number (reference)	Study design	Study duration	Patient population	Intervention	Comparator	Outcomes and follow-up period
Clarity AD, NCT03887455	Phase 3, placebo-controlled, double-blind, parallel-group 18-month study with an open-label extension	Core Study: 41 months (FPI 27 Mar 2019 to LPO 25 Aug 2022), treatment duration was 18 months OLE Study: up to 48 months	Adult patients with MCI due to AD or Mild AD	Lecanemab (IV), 10 mg/kg biweekly	Placebo (IV) biweekly	**Core Study**: all primary and secondary outcomes were measured up until 18 months; CDR-SB; ADAS-Cog14, ADCOMS, ADCS MCI-ADL, Safety **OLE Study**: Additional 18 months of follow-up available (36 months in total); CDR-SB, Safety

Source: Clarity AD CSR (68)

Abbreviations: AD = Alzheimer's disease; ApoE ε4 = apolipoprotein E4; CDR-SB = Clinical Dementia Rating–Sum of Boxes; FPI = first patient in; LPO = last patient out; MCI = mild cognitive impairment; 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 Scale for Mild Cognitive Impairment

6.1.2 Comparability of studies

N/A

6.1.2.1 Comparability of patients across studies

For the Core Study, baseline demographics and characteristics of the ITT FAS+ for ApoE ε4 non-carriers and heterozygotes are shown in Table 12. Similarly, for the OLE Phase, baseline characteristics of the 1366 patients in the lecanemab-treated period (Core Study and OLE Phase in which patients received lecanemab 10 mg/kg biweekly) are also presented in Table 12.

As shown in Table 12, the baseline characteristics of both the Core Study and OLE Phase were broadly similar across all arms. Of note, the proportion of non-carriers (Core Study: lecanemab = 36.9% [267/723] vs placebo =. 37.0% [275/743]; OLE Phase= 36.4% [497/1366]) and heterozygotes (Core Study: lecanemab = 63.1% [456/723] vs. placebo = 63.0% [468/743]; OLE Phase = 63.6% [869/1366]) was balanced across all groups. In the Core Study, 61.5% (445/723) of lecanemab and 62.2% (462/743) of placebo participants were MCI due to AD and 38.5% (278/723) of lecanemab and 37.8% (281/743) of placebo patients were mild dementia due to AD. In the OLE Phase 62.6% (855/1366) participants had MCI due to AD and 37.4% (511/1366) had mild dementia due to AD at baseline. Baseline values for clinical outcome scores (CDR-SB, ADAS-Cog14, ADCOMS, ADCS MCI-ADL, and MMSE) were consistent between all groups.

Table 12 Baseline characteristics of patients in studies included for the comparative analysis of efficacy and safety (Core Study, FAS+; OLE Phase, lecanemab-treated period, safety analysis set), ApoE ε4 Non-carriers and Heterozygotes

	Clarity AD Core Study		Clarity AD OLE Phase
	Lecanemab (n=723)	Placebo (n=743)	Lecanemab 10 mg/kg Biweekly (n=1366)
Age in years, mean (SD)	72.1 (7.9)	71.4 (8.0)	[redacted]
Age group, n (%)			
<65 years	127 (17.6)	148 (19.9)	[redacted]
≥65 years	596 (82.4)	595 (80.1)	[redacted]
≥65, <75 years	291 (40.2)	300 (40.4)	[redacted]
≥75 years	305 (42.2)	295 (39.7)	[redacted]
Female, n (%)	365 (50.5)	380 (52.5)	[redacted]
Race, n (%)			
White	557 (77.0)	584 (78.6)	[redacted]
Black or African American	16 (2.2)	17 (2.3)	[redacted]
Asian	120 (16.6)	119 (16.0)	[redacted]
American Indian or Alaskan Native	0	1 (0.1)	[redacted]
Other	17 (2.4)	10 (1.3)	[redacted]
Missing	13 (1.8)	12 (1.6)	[redacted]
Clinical subgroup (CRF), n (%)			
MCI due to AD	445 (61.5)	462 (62.2)	[redacted]
Mild dementia	278 (38.5)	281 (37.8)	[redacted]

	Clarity AD Core Study		Clarity AD OLE Phase
	Lecanemab (n=723)	Placebo (n=743)	Lecanemab 10 mg/kg Biweekly (n=1366)
ApoE ε4 status (Laboratory), n (%)			
Heterozygous carrier	456 (63.1)	468 (63.0)	[redacted]
Non-carrier	267 (36.9)	275 (37.0)	[redacted]
Use of AD symptomatic medication at baseline as per CRF, n (%)			
Yes	374 (51.7)	399 (53.7)	[redacted]
No	349 (48.3)	344 (46.3)	[redacted]
CDR-SB, mean (SD)	3.17 (1.34)	3.22 (1.35)	[redacted]
ADAS-Cog14, mean (SD)	24.51 (7.03)	24.40 (7.57)	[redacted]
ADCOMS, mean (SD)	0.398 (0.146)	0.400 (0.148)	[redacted]
ADCS-MCI-ADL, mean (SD)	41.2 (6.6)	40.8 (7.0)	[redacted]
MMSE, mean (SD)	25.5 (2.2)	25.6 (2.2)	[redacted]
Amyloid PET burden in Centiloids, mean (SD)	76.252 (46.026)	73.742 (42.047)	[redacted]

Sources: Eisai DOF (Table 14.1.4.1.1allnh, Table 14.1.4.1.4allnh) (83); Eisai DOF (301 Core Baseline Summary Indicated Population) (85); Source: Eisai DOF (Table 14.1.4.1.1nh (86) , Table 14.1.4.1.7nh (87)).
Abbreviations: AD = Alzheimer's Disease; ApoE ε4 = Apolipoprotein E4; ADAS-Cog14 = Alzheimer's Disease Assessment Scale - Cognitive Subscale 14-item version, ADCOMS = Alzheimer's Disease Composite Score; ADCS MCI-ADL = Alzheimer's Disease Cooperative Study-Activities of Daily Living Scale for Mild Cognitive Impairment, CDR-SB = Clinical Dementia Rating – Sum of Boxes, CRF = Case report form; MCI = Mild cognitive impairment; MMSE = Mini Mental State Examination; SD = Standard deviation
Lecanemab Treated Period includes Core Study and OLE Phase in which subjects received lecanemab 10 mg/kg biweekly. Baseline is the last non-missing assessment prior to the start of the period. Specifically, baseline is the OLE baseline for subjects who received lecanemab 10 mg/kg biweekly from the OLE phase and is the Core Study baseline for subjects who received lecanemab 10 mg/kg biweekly from the Core Study. Percentages are based on the total number of subjects in the relevant treatment group. Data collected after subjects switch to/start subcutaneous dose are not included.

6.1.3 Comparability of the study population(s) with Danish patients eligible for treatment

Table 13 Characteristics in the relevant Danish population and in the health economic model

	Value in Danish population (reference)	Value used in health economic model Clarity AD CSR (50, 81)
Age (mean, SD)	n/a (Expected similar to Clarity AD population)	71.8 (8.0)
Gender (female%)	54% (46)	51.5%

6.1.4 Efficacy – results per Clarity AD Core Study

The following section describes the primary, secondary and key exploratory efficacy endpoints from the Clarity AD Core study. Other exploratory and biomarker endpoints which are relevant to understand the clinical value of lecanemab have been provided in Appendix K. A summary of the clinical data and meaningful benefit of lecanemab, which considers the totality of the evidence provided in this dossier, is described in Appendix M.

All efficacy and safety analyses presented in this dossier are based on the patients who were on IV lecanemab or placebo. All efficacy analyses were performed for the subgroup of patients who are ApoE ε4 non-carriers and heterozygotes in the ITT FAS+ set based on the data cut-off from September 13th, 2022 (50, 81).

All 'change from baseline' results were analysed using Mixed Model Repeated Measures (MMRM). 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 (50, 81). The combined ApoE ε4 non-carrier and heterozygous subpopulation can be considered a post-hoc analysis but was considered appropriate by the EMA based on the analysis of the pre-specified strata. While genotype was not a stratification factor, the proportion of ApoE ε4 noncarriers and heterozygotes were balanced across both arms and the sample size remains high (lecanemab = 723; placebo = 743). The highly statistically significant results for all endpoints were also confirmed by sensitivity analyses exploring the missing at random assumption.

Sensitivity analyses were conducted (the descriptions of which are provided in Appendix K.2.1) and the results provided in the EMA SmPC for CDR-SB, ADAS-Cog14 and ADCS MCI-ADL are based on the "Copy Increments from Control Based Imputation approach" sensitivity analysis, the results of which are consistent with that of the primary efficacy analysis, demonstrating the robustness of the primary analysis. Results of the sensitivity analyses can be found in Appendix K.2.2.

6.1.4.1 Primary outcome

6.1.4.1.1 CDR-SB

In ApoE ε4 non-carriers and heterozygotes, the mean CDR-SB scores at baseline were comparable (3.17 in the lecanemab group and 3.22 in the placebo group). At 18 months, patients who received lecanemab experienced 33.5% less decline in mean CDR-SB from

baseline compared to placebo (change from baseline: 1.15 vs 1.73, respectively), representing a statistically significant adjusted mean difference of -0.58 (95% CI: -0.81, -0.35; p<0.0001; Table 14). Starting as early as 3 months and across all subsequent time points, lecanemab-treated patients demonstrated increasingly statistically significant changes in CDR-SB from baseline compared to placebo (3 months: p<0.05; 6 months: p<0.01; 9 months: p<0.001; 12-18 months: p<0.0001; Figure 7), accompanied by an increase in the absolute treatment difference over time (88).

Furthermore, at 18 months, lecanemab had a consistent effect on patients' symptoms across all CDR-SB domains including memory, orientation, judgment, community activities, hobbies, and personal care (Figure 8) (89). These six domains of cognition (memory, orientation, judgment/problem solving) and function (community affairs, home/hobbies, personal care) have been identified by patients and caregivers as important measures of autonomy and sense of self.

Additional subgroup analyses of CDR-SB were conducted and are described in Appendix K.3.1. The sensitivity and supplementary analyses of CDR-SB are described in Appendix K.2.2.1.

Table 14 Change from baseline in CDR-SB at 18 months; Clarity AD Core Study (FAS+), ApoE ε4 Non-carriers and Heterozygotes

Statistic	Lecanemab (n=723)	Placebo (n=743)
N analysed	[redacted]	[redacted]
n analysed	[redacted]	[redacted]
Mean (SD) at baseline	3.17 (1.342)	3.22 (1.353)
Adjusted mean change from baseline (SE)	1.151[redacted]	1.730[redacted]
Adjusted mean change from baseline (95% CI); p-value	-0.579 (-0.811, -0.347); p<0.001	
Adjusted percentage difference vs placebo	-33.5%	
Absolute mean at 18 months (SD)	[redacted]	[redacted]
Absolute mean change from baseline	[redacted]	[redacted]
Absolute difference in mean at 18 months	[redacted]	
Absolute percentage difference vs placebo	[redacted]	

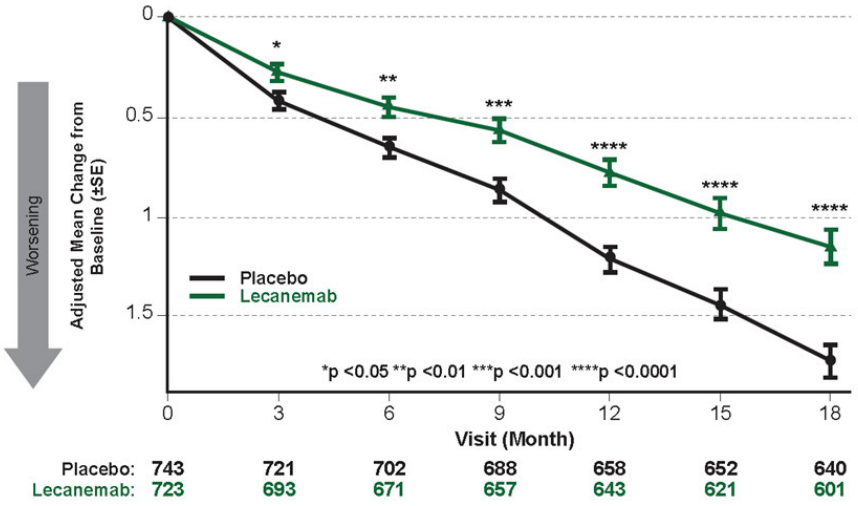
Source: Eisai DOF (Table 14.2.1.1.2nh) (89); Perry et al., 2024 (88); EMA SmPC (1); Eisai DOF (301COREOLE_36m_simple summary statistics indicated population) (90)

Abbreviations: ApoE ε4 = Apolipoprotein E4; CDR-SB = Clinical Dementia Rating Sum of Boxes; SE = Standard Error

Note: Based on modified intention-to-treat analysis population. Adjusted mean change from baseline, SE and p-value are derived using mixed model repeat measures with treatment group, visit, treatment group by visit interaction, clinical subgroup, use of Alzheimer's disease symptomatic medication at baseline, ApoE ε4 carrier status, region, baseline value by visit interaction as fixed effects, and baseline value as covariate.

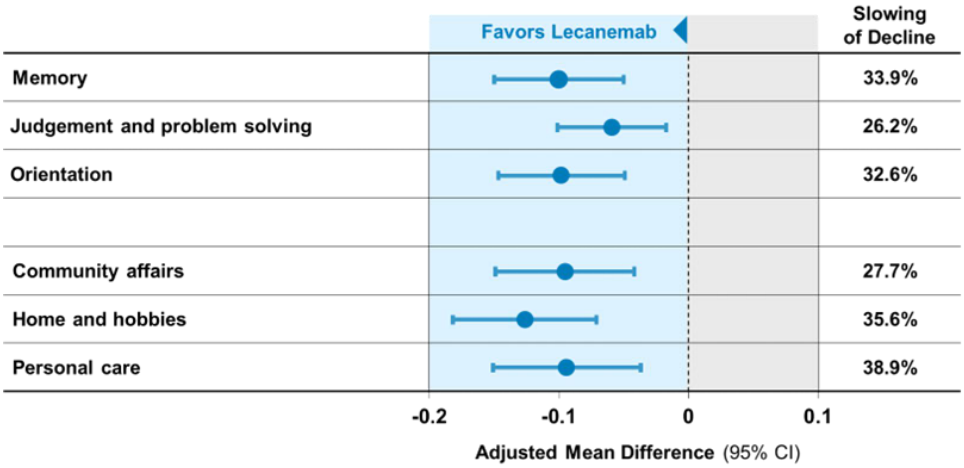
N shows the number of subjects who are included in MMRM and is the same across all visits. n shows the number of subjects at 18 months.

Figure 7 Change from Baseline to 18 Months, Mean CDR-SB; Clarity AD Core Study (FAS+), ApoE ε4 Non-carriers and Heterozygotes



Source: Perry et al., 2024 (88)
Abbreviations: ApoE ε4 = Apolipoprotein E4; CDR-SB = Clinical Dementia Rating Sum of Boxes; SE = Standard Error
Note: Based on modified intention-to-treat analysis population. Adjusted mean change from baseline, SE and p-value are derived using mixed model repeat measures with treatment group, visit, treatment group by visit interaction, clinical subgroup, use of Alzheimer's disease symptomatic medication at baseline, ApoE ε4 carrier status, region, baseline value by visit interaction as fixed effects, and baseline value as covariate.

Figure 8 Individual CDR-SB Domain Analysis at 18 Months; Clarity AD Core Study (FAS+), ApoE ε4 Non-carriers and Heterozygotes



Source: Eisai DOF (89)
Abbreviations: AD = Alzheimer's Disease; ApoE ε4 = Apolipoprotein E4; CDR-SB = Clinical Dementia Rating Sum of Boxes; CI = Confidence Interval

6.1.4.2 Secondary outcomes

6.1.4.2.1 Amyloid PET using Centiloids

Among the 352 (173 lecanemab and 179 placebo) patients who were included in the amyloid PET analyses for ApoE ε4 non-carriers and heterozygotes at 18 months, the mean amyloid level at baseline was similar [redacted] Centiloids in the lecanemab group and [redacted] Centiloids in the placebo group) (Table 15) (91). At 18 months, the mean amyloid PET level for the lecanemab group was [redacted] Centiloids, while the average amyloid level in the placebo group was [redacted] Centiloids (91). The mean amyloid PET level for the lecanemab group at 18 months is below the threshold for amyloid negativity of approximately30

Centiloids, which is considered a 'normal' level, above which patients are considered to have elevated or 'higher than normal' brain amyloid (92).

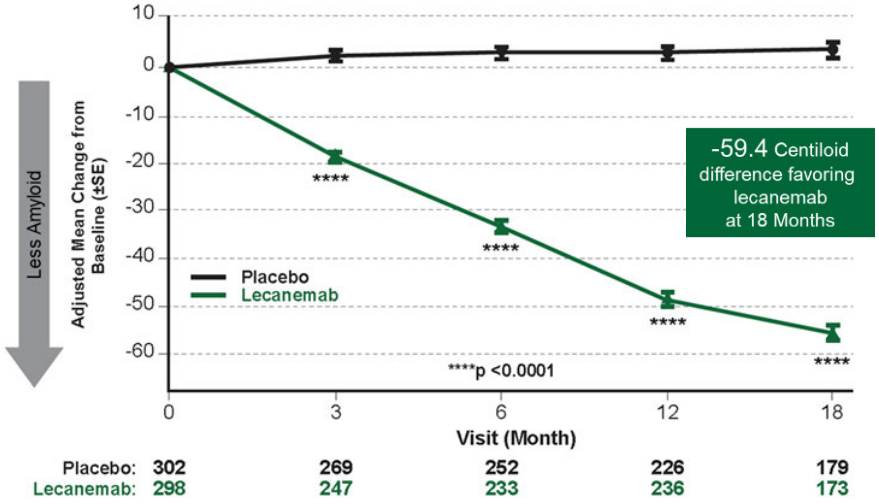
Patients who received lecanemab experienced a statistically significant reduction in amyloid burden compared to placebo, with a mean change from baseline of [redacted] CL for lecanemab versus [redacted] CL for placebo (mean change from baseline: -59.437 CL; p<0.00001; Figure 9; Table 15) (3). Of note, the magnitude of the reduction increased over time, with reductions in Aβ burden versus placebo seen starting as early as 3 months following lecanemab treatment (88).

Table 15 Change in Amyloid PET (Centiloids) through 18 Months from baseline; Clarity AD Core Study (PD analysis set), ApoE ε4 Non-carriers and Heterozygotes

Statistic	Lecanemab	Placebo
N analysed	[redacted]	[redacted]
n analysed	[redacted]	[redacted]
Mean (SD) at baseline	[redacted]	[redacted]
Adjusted mean change from baseline (SE)	[redacted]	[redacted]
Adjusted mean change from baseline (95% CI); p-value	-59.437 [redacted]	p<0.00001
Adjusted percentage difference vs placebo	NR	
Absolute mean at 18 months (SD)	[redacted]	[redacted]
Absolute mean change from baseline	[redacted]	[redacted]
Absolute difference in mean at 18 months	[redacted]	

Source: Eisai DOF (T.14.2.2.1.1nh) (91); Eisai DOF (3); Perry et al., 2024 (88); Eisai DOF (301COREOLE_36m_simple summary statistics indicated population) (90)
Abbreviations: PD = pharmacodynamic; SD = standard deviation.
N shows the number of subjects who are included in MMRM and is the same across all visits. n shows the number of subjects at 18 months.

Figure 9 Change in Amyloid PET (Centiloids) Through 18 Months from Baseline; Clarity AD Core Study (PD Analysis Set), ApoE ε4 Non-carriers and Heterozygotes



Source: Perry et al., 2024 (88)
Statistical significance was confirmed at 3 months, 6 months, 12 months, and at 18 months (all P<0.00001)
Abbreviations: AD = Alzheimer's Disease; ApoE ε4 = Apolipoprotein E4; PD = Pharmacodynamic; PET = Positron Emission Tomography; SE = Standard Error
Note: Based on pharmacodynamic analysis population (amyloid PET substudy population). Adjusted mean change from baseline, standard error (SE) and p-value are derived using mixed model repeat measures (MMRM) with treatment group, visit, treatment group by visit interaction, clinical subgroup, use of Alzheimer's disease symptomatic medication at baseline, ApoE ε4 carrier status, region, baseline value by visit interaction as fixed effects, and baseline value as covariate. 73 subjects were not included at 18 months (per Statistical analysis plan) since their PET assessments were performed after receiving lecanemab in the extension phase.

6.1.4.2.1 Patients converting to amyloid negativity

In the ApoE ε4 non-carrier and heterozygote population, there was a statistically significant difference between lecanemab and placebo in the proportion of patients who converted to amyloid negativity (by amyloid PET in Centiloids) (93). A statistically significant difference was observed as early as three months between lecanemab-treated and placebo patients (lecanemab [redacted] versus placebo [redacted] This statistically significant difference was maintained through to 18 months of treatment, where only [redacted] of patients receiving placebo achieved amyloid negativity at 18 months compared to [redacted] of patients who received lecanemab [redacted] (93, 94).

[redacted]

Source: Eisai DOF (93)
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
Abbreviations: PD = Pharmacodynamic; PET = Positron Emission Tomography; SE = Standard Error

6.1.4.2.2 ADAS-Cog14

In the ApoE ε4 non-carrier and heterozygote population, the adjusted mean change from baseline at 18 months in the ADAS-Cog14 score was 4.211 in the lecanemab group and 5.845 in the placebo group (83). The adjusted mean difference for lecanemab compared to placebo at 18 months was statistically significant (-1.633; 95% CI: -2.555, -0.712; p=0.00052), equating to 27.9% less decline in ADAS-Cog14 (Table 16, Figure 11) (83). Starting as early as six months, lecanemab showed statistically significant (p<0.05) changes from baseline compared to placebo and at all subsequent timepoints, these changes were

statistically significant (p<0.0001; at 18 months p=0.00052). The changes from baseline compared to placebo also tended to increase over time.

The effect of lecanemab was consistent across most ADAS-Cog14 domains (Figure 12) (89). These results indicate that lecanemab treated patients exhibited less decline in cognition, executive function, and verbal recall, in comparison to placebo treated patients. A delay in decline on the ADAS-Cog14 reflects, amongst other elements, extended maintenance of executive function and spoken language ability and comprehension, which can prolong independence for patients and maintain quality of life (61, 95). The sensitivity and supplementary analyses of ADAS-Cog14 are described in Appendix K.2.2.2.

Table 16 Change from baseline in ADAS-Cog14 at 18 months; Clarity AD Core Study (FAS+), ApoE ε4 Non-carriers and Heterozygotes

Statistic	Lecanemab (n=723)	Placebo (n=743)
N analysed	[redacted]	[redacted]
n analysed	[redacted]	[redacted]
Mean (SD) at baseline	24.48 (6.987)	24.40 (7.572)
Adjusted mean change from baseline (SE)	4.211[redacted]	5.845[redacted]
Adjusted mean change from baseline (95% CI); p-value	-1.633 (-2.555, -0.712); p<0.001	
Adjusted percentage difference vs placebo	-27.9%	
Absolute mean at 18 months(SD)	[redacted]	[redacted]
Absolute mean change from baseline	[redacted]	[redacted]
Absolute difference in mean at 18 months	[redacted]	
Absolute percentage difference vs placebo	[redacted]	

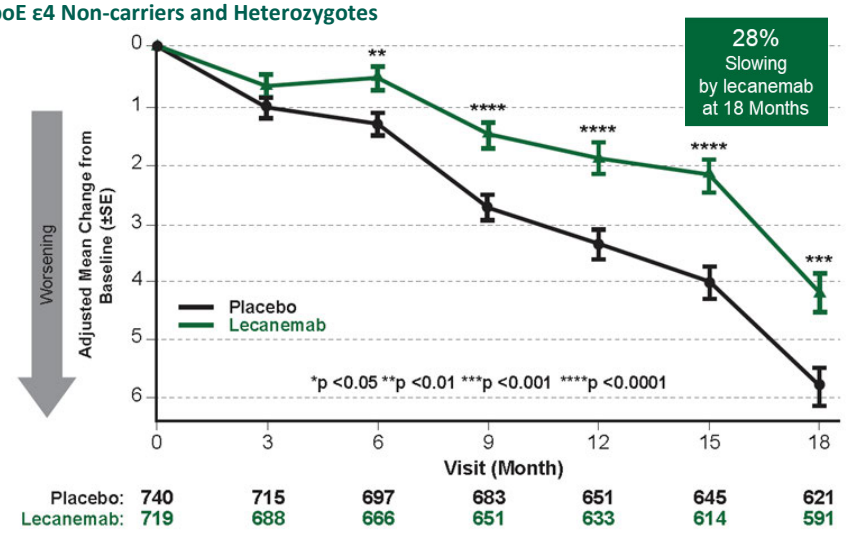
Source: Eisai DOF (Table 14.2.2.2.2nh) (83); Perry et al., 2024 (88); EMA SmPC (1), Eisai DOF (301COREOLE_36m_simple summary statistics indicated population) (90)

Abbreviations: ADAS-Cog14 = Alzheimer's Disease Assessment Scale – Cognitive subscale 14-item version; CI = Confidence interval; FAS = Full Analysis Set; ITT = intent-to-treat; SE = standard error.

Note: Based on modified intention-to-treat analysis population. Adjusted mean change from baseline, SE and p-value are derived using mixed model repeat measures with treatment group, visit, treatment group by visit interaction, clinical subgroup, use of Alzheimer's disease symptomatic medication at baseline, ApoE ε4 carrier status, region, baseline value by visit interaction as fixed effects, and baseline value as covariate.

N shows the number of subjects who are included in MMRM and is the same across all visits. n shows the number of subjects at 18 months.

Figure 11 Change in ADAS-Cog14 Score from Baseline to 18 Months; Clarity AD Core Study (FAS+), ApoE ε4 Non-carriers and Heterozygotes



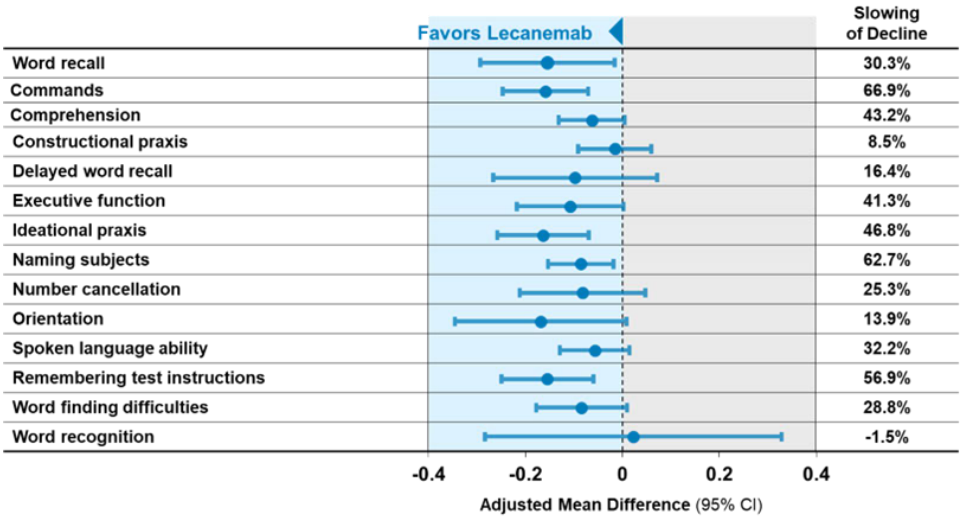
Source: Perry et al., 2024 (88)

Abbreviations: AD = Alzheimer's Disease; ADAS-cog14= Alzheimer's Disease Assessment Scale – Cognitive Subscale 14; ApoE ε4 = Apolipoprotein E4; SE = Standard Error

Statistical significance was confirmed at 6 months (P<0.05), 9 months (P<0.0001), 12 months (P<0.0001), 15 months (P<0.0001), and at 18 months (P<0.001).

Note: Based on modified intention-to-treat analysis population. Adjusted mean change from baseline, SE and p-value are derived using mixed model repeat measures (MMRM) with treatment group, visit, treatment group by visit interaction, clinical subgroup, use of Alzheimer's disease symptomatic medication at baseline, ApoE ε4 carrier status, region, baseline value by visit interaction as fixed effects, and baseline value as covariate.

Figure 12 Individual ADAS-Cog14 Domain Analysis at 18 Months; Clarity AD Core Study (FAS+), ApoE ε4 Non-carriers and Heterozygotes



Source: Eisai DOF(89)

Abbreviations: AD = Alzheimer's Disease; ADAS-Cog14 = Alzheimer's Disease Assessment Scale – Cognitive Subscale 14; ApoE ε4 = Apolipoprotein E4; CI = Confidence Interval.

6.1.4.2.3 ADCS MCI-ADL

In the ApoE ε4 non-carrier and heterozygote population, the adjusted mean change from baseline at 18 months in ADCS MCI-ADL was -3.469 in the lecanemab group and 5.703 in the placebo group (83). The adjusted mean difference for lecanemab compared to placebo at 18 months was statistically significant (2.234; 95% CI: 1.342, 3.126; p<0.00001),

equating to 39.2% less decline in ADCS MCI-ADL (Figure 13; Table 17) (83). At six months, the earliest assessment timepoint, lecanemab showed statistically significant changes ($p<0.01$) in ADCS MCI-ADL from baseline compared to placebo, with increasing significance at 12 months which was maintained to 18 months ($p<0.00001$). The changes from baseline compared to placebo increased over time for the duration of the study (83).

Breakdown of the ADCS MCI-ADL Individual Item Score demonstrates the everyday activities (e.g., cleaning, making appointments with friends, making phone calls, cooking meals, managing money, etc.) in which patients receiving lecanemab were able to maintain for longer in comparison to those who received placebo (Figure 14) (89). Maintaining activities of daily living is crucial for patients as they enable them to remain independent for an extended period, whilst also reducing caregiving responsibilities and caregiver burden (96). The sensitivity and supplementary analyses of ADCS MCI -ADL are described in Appendix K.2.2.3.

Table 17 Change from baseline in ADCS MCI-ADL at 18 months; Clarity AD Core Study (FAS+), ApoE ε4 Non-carriers and Heterozygotes

Statistic	Lecanemab (n=723)	Placebo (n=743)
N analysed	[redacted]	[redacted]
n analysed	[redacted]	[redacted]
Mean (SD) at baseline	41.3 (6.52)	40.9 (6.82)
Adjusted mean change from baseline (SE)	-3.469[redacted]	-5.703[redacted]
Adjusted mean change from baseline (95% CI); p-value	2.234 (1.342, 3.126); p<0.00001	
Adjusted percentage difference vs placebo	-39.2%	
Absolute mean at 18 months(SD)	[redacted]	[redacted]
Absolute mean change from baseline	[redacted]	[redacted]
Absolute difference in mean at 18 months	[redacted]	
Absolute percentage difference vs placebo	[redacted]	

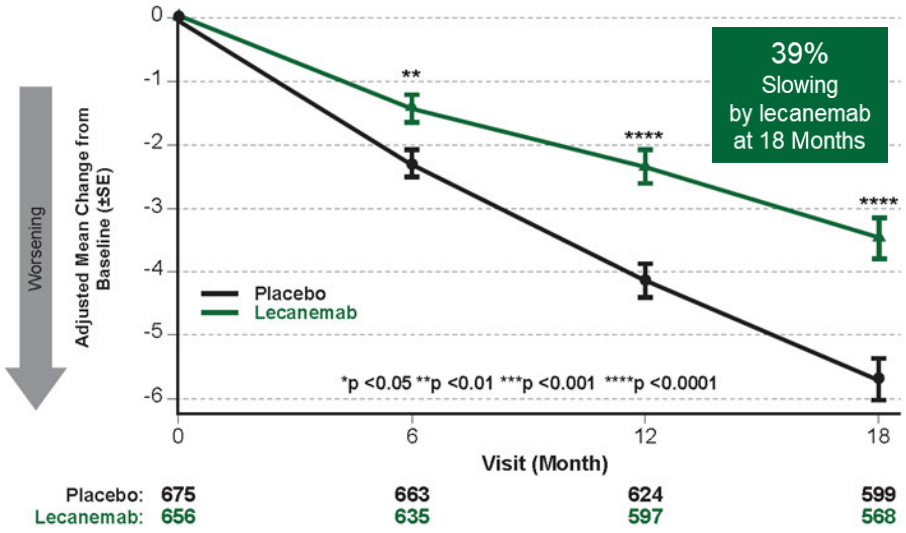
Source: Eisai DOF (Table 14.2.2.4.2nh) (83); Perry et al., 2024 (88); EMA SmPC (1) , Eisai DOF (301COREOLE_36m_simple summary statistics indicated population) (90)

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; SE = standard error.

Note: Based on modified intention-to-treat analysis population. Adjusted mean change from baseline, SE and p-value are derived using mixed model repeat measures with treatment group, visit, treatment group by visit interaction, clinical subgroup, use of Alzheimer's disease symptomatic medication at baseline, ApoE ε4 carrier status, region, baseline value by visit interaction as fixed effects, and baseline value as covariate.

N shows the number of subjects who are included in MMRM and is the same across all visits. n shows the number of subjects at 18 months.

Figure 13 Change in ADCS-MCI-ADL Score Through 18 Months from Baseline in Clarity AD Core Study (FAS+), ApoE ε4 Non-carriers and Heterozygotes



Source: Perry et al., 2024 (88)

Abbreviations: AD = Alzheimer's Disease; ADCS-MCI-ADL = Alzheimer's Disease Cooperative Study-Activities of Daily Living Inventory Mild Cognitive Impairment Version; ApoE ε4 = Apolipoprotein E4; SE = Standard Error

Statistical significance was confirmed at 6 months (P<0.01), 12 months (P<0.00001), and at 18 months (P<0.00001)

Note: Based on modified intention-to-treat analysis population. Adjusted mean change from baseline, SE and p-value are derived using mixed model repeat measures (MMRM) with treatment group, visit, treatment group by visit interaction, clinical subgroup, use of Alzheimer's disease symptomatic medication at baseline, ApoE ε4 carrier status, region, baseline value by visit interaction as fixed effects, and baseline value as covariate.

[redacted]

Source: Eisai DOF (89)

Abbreviations: AD = Alzheimer's Disease; ADCS-MCI-ADL = Alzheimer's Disease Cooperative Study-Activities of Daily Living Inventory Mild Cognitive Impairment Version; ApoE ε4 = Apolipoprotein E4; CI = Confidence Interval

6.1.4.3 Key exploratory outcomes

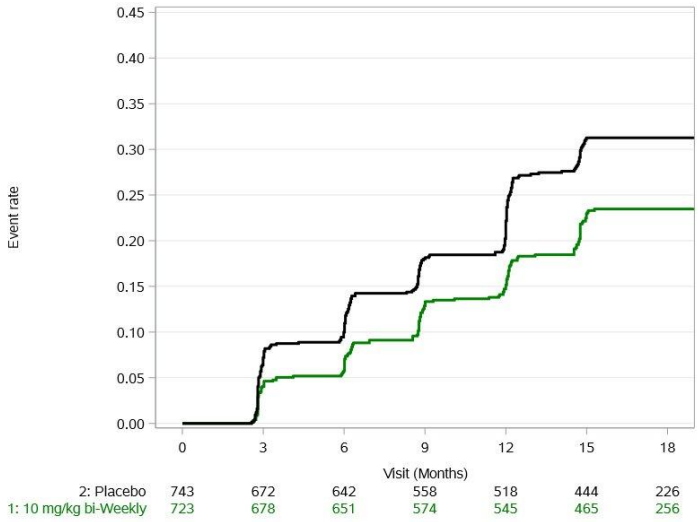
6.1.4.3.1 TTW of CDR-SB at 18 months

Time to worsening (TTW) of CDR-SB is an exploratory analysis of the primary efficacy outcome and provides additional context to the results. The TTW for Global CDR is also described in Appendix K.4.1.

The worsening of CDR-SB was defined as the CDR-SB score increasing from MCI due to AD at baseline to a worse AD severity level (mild, moderate, or severe AD), or mild AD at baseline to a worse AD severity level (moderate or severe AD) based on the first worsening where a worsening is observed in 2 consecutive visits. AD severity level was defined by CDR-SB scores (MCI due to AD: 0.5-4.0; mild AD: 4.5-9.0; moderate AD: 9.5-15.5; severe AD: 16.0-18.0).

At 18 months, lecanemab showed a 30.2% reduction in the risk of progression to the next stage of AD on the CDR-SB score (HR: 0.698, 95% CI: 0.568, 0.858, p=0.00062) in ApoE ε4 non-carriers and heterozygotes (Figure 15) (97). Subgroup analyses by AD dementia stages are presented in Appendix K.4.1.

Figure 15 TTW of CDR-SB Scores up to 18 Months; Clarity AD Core Study (FAS+), ApoE ε4 Non-carriers and Heterozygotes



Source: Eisai DOF (Time to worsening_nh_Core) (97)
Abbreviations: AD = Alzheimer's disease; ApoE ε4 = Apolipoprotein E4; CDR = Clinical Dementia Rating.

6.1.5 Efficacy – results per Clarity AD OLE Study

The following section describes the primary efficacy endpoint, CDR-SB, from the Clarity AD OLE trial. For additional secondary and exploratory endpoints, please see Appendix L.1 - L.3. The efficacy results in Section 6.1.5.1 provide 18 months of follow-up data (36 months including the Clarity AD Core Study) (98).

Interim efficacy results in Section 6.1.5.2 provide 30 months of follow-up data (48 months including the Clarity AD Core Study) (99).

6.1.5.1 CDR-SB at 36 months

The combined Clarity AD Core Study and OLE data show that lecanemab treatment results in accumulating benefit compared to natural disease progression through 36 months (Core + 18 months) in ApoE ε4 non-carriers and heterozygotes.

A modelled placebo group based on an observational cohort (Alzheimer's Disease Neuroimaging Initiative [ADNI]) for CDR-SB is used to provide context since there is no placebo control group between 18 and 48 months. An a-priori matched observational cohort from ADNI (matched on baseline demographics and clinical characteristics) was created during the design of Clarity AD to aid in decision-making for the protocol design (for estimations of placebo decline to aid in power calculations, among others). The

criteria used to match the ADNI observational cohort to the Clarity AD patient population included the following:

1. Baseline diagnosis:
   a. "MCI" with the global Clinical Dementia Rating (CDR) score=0.5 and CDR memory ≥0.5, or
   b. "AD" with global CDR=0.5 or 1.0 and CDR memory ≥0.5;
2. Proportion of MCI (60%) and mild AD (40%)
3. Baseline Mini–Mental State Exam (MMSE) score ≥22;
4. At least 1 of 2 criteria for amyloid positivity:
   a. baseline amyloid PET standardized uptake value ratios (SUVr) florbetapir ≥1.11 or amyloid PET SUVr Pittsburgh compound B (PIB) ≥1.47, or
   b. baseline cerebrospinal fluid (CSF) total tau/amyloid beta (Aβ) >0.222.

The ADNI-matched cohort report, which details the methodology, matching criteria and results is described in Appendix L.4.

As shown in Figure 16, matched data from ADNI very closely aligns with placebo in Clarity AD for the 18-month Core Study, providing confidence that the matching criteria was successful, and thus confirming it could be used as a historical control for the OLE period. This is relevant since there is no longer a true placebo arm to compare to, given all patients receive active treatment after 18 months. Recognizing the limitations of using an external control, the treatment effect between lecanemab treatment and the natural history cohort continues to increase from 18 through 36 months (absolute treatment difference: [redacted] [18 months], [redacted] [30 months], [redacted] [36 months]), illustrating cumulative benefit from lecanemab treatment compared to natural disease progression (98). This analysis signifies that the slowing of disease progression seen at 18 months with lecanemab versus placebo is maintained, and that the trajectory of disease decline is meaningfully altered by treatment with lecanemab over the long term.

Results from the full population of Clarity AD (i.e., patients with MCI due to AD or mild AD patients who are ApoE ε4 noncarriers, homozygotes or heterozygotes) are presented in Appendix L.1.

[redacted]

Source: Eisai DOF (98)
Abbreviations: ADNI = Alzheimer's Disease Neuroimaging Initiative; ApoE ε4 = Apolipoprotein E4; CDR-SB: Clinical Dementia Rating Sum of Boxes; IV: Intravenous; OLE: Open-Label Extension; SE: Standard Error

6.1.5.2 CDR-SB at 48 months

In line with the results from the 36 month OLE, cumulative treatment effects continue to expand between lecanemab and natural history cohort from 18 through to 48 months (absolute treatment difference: [redacted] [18 months], [redacted] [30 months], [redacted] [36 months], [redacted] [48 months]) (99).

[redacted]

Source: Eisai DOF (99)

Abbreviations: ADNI = Alzheimer's Disease Neuroimaging Initiative; ApoE ε4 = Apolipoprotein E4; CDR-SB: Clinical Dementia Rating Sum of Boxes; IV: Intravenous; OLE: Open-Label Extension

7. Comparative analyses of efficacy

7.1.1 Differences in definitions of outcomes between studies

N/A

7.1.2 Method of synthesis

N/A

7.1.3 Results from the comparative analysis

Overall key results are presented below.

Table 18 Results from the comparative analysis of lecanemab vs placebo for early AD patients who are ApoE ε4 Non-carriers and Heterozygotes

Outcome measure	Lecanemab (N=723)	Placebo (N=743)	Result
Change from baseline in CDR-SB, 18 months	1.151 (0.087)	1.730 (0.085)	Mean difference: -0.579 (-0.811, -0.347); p<0.001
Change in Amyloid PET (Centiloids) from baseline, 18 months	-55.541 (1.606)	3.895 (1.608)	Mean difference: -59.437 (-63.291, -55.582); p<0.00001
Proportion of patients who become amyloid negative, 18 months	[redacted]	[redacted]	N/A,[redacted]
Change from baseline in ADAS-Cog14, 18 months	4.211 (0.347)	5.845 (0.342)	Mean difference: -1.633 (-2.555, -0.712); p<0.001
Change from baseline in ADCS-MCI-ADL, 18 months	-3.469 (0.342)	-5.703 (0.337)	Mean difference: 2.234 (1.342, 3.126); p<0.00001
TTW of CDR-SB, 18 months	N/A	N/A	HR: 0.698, 95% CI: 0.568, 0.858, p=0.00062
Outcome measure	**Early Start (N=743)**	**ADNI (N=346)**	**Result**
Change from baseline in CDR-SB, 36 months	[redacted]	[redacted]	Mean difference: -[redacted]
Change from baseline in CDR-SB, 48 months	4.400	5.708	Mean difference: -1.31

7.1.4 Efficacy – results per [outcome measure]

N/A

8. Modelling of efficacy in the health economic analysis

Data used to estimate AD progression in the economic model is based on Clarity AD integrated with natural history data derived from the literature as follows: For the SoC arm, Clarity AD data for the first 18 months (section 8.1.1), natural history of the disease thereafter (section 8.2.1); for the Lecanemab arm, Clarity AD data (section 8.1.1), HR derived from Clarity AD data applied to natural history of the disease thereafter (section 8.1.2). A scenario was tested using natural history of the disease from model start, instead of after 18 months.

As Clarity AD did not include overall survival as an endpoint, and did not include information on institutionalisation, these are informed by the published literature (section 8.2.2 and 8.2.3) and applied in the model by health state. The complete overview of source and values of the transition probabilities (TPs) applied in the model is provided in section 8.2.4.1.

8.1 Presentation of efficacy data from the clinical documentation used in the model

8.1.1 AD progression in the first 18 months

Clarity AD data were applied in the model to estimate disease progression for both the lecanemab and the SoC arm during the first 18 months of the time horizon. In the economic model, the 18-month health state occupancies derived from Clarity AD (Table 19) were converted to one-month TPs, assuming the TPs were constant during the first 18 months (see section 8.2.4).

Table 19 Health state occupancy as defined by CDR-SB at last assessment; Clarity AD (FAS+), ApoE ε4 non-carriers and heterozygotes

	MCI due to AD	Mild AD	Moderate AD	Severe AD
Lecanemab, n (%)				
ITT FAS+ (n=714)	[redacted]	[redacted]	[redacted]	[redacted]
MCI due to AD (n=564)	[redacted]	[redacted]	[redacted]	[redacted]
Mild AD (n=150)	[redacted]	[redacted]	[redacted]	[redacted]
Placebo, n (%)				
ITT FAS+ (n=737)	[redacted]	[redacted]	[redacted]	[redacted]
MCI due to AD (n=577)	[redacted]	[redacted]	[redacted]	[redacted]
Mild AD (n=160)	[redacted]	[redacted]	[redacted]	[redacted]

Source: Clarity AD CSR (68)

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

Note: ITT-FAS+ identifies randomized subjects who received at least 1 dose of study drug, and who had a baseline assessment and at least one post dose primary efficacy measurement.

8.1.2 Lecanemab treatment effect vs natural history used after 18-months

Lecanemab treatment effect was estimated applying a constant HR versus SoC, derived from the Clarity AD TTW analysis. The TTW analyses presented in the clinical section (section 6.1.4.3.1 for the Core data and in Appendix L.3.1 for OLE) censored subjects upon

death and discontinuation. A control-based multiple imputation approach with copy-increments was applied to estimate the impact of all-cause discontinuation on the resulted HR for the combined population (MCI due to AD and Mild AD) and was used in the economic analysis base case.

In the copy increment approach, all data in the placebo group were used to build the imputation model for each visit using a regression model. After the placebo imputation model was built, the changes between visits were used to impute missing values in the lecanemab group. This approach may be considered conservative as placebo values are used to impute missing values in the lecanemab group. Figure 18 shows the resulting KM for the combined population. The resulting HR was [redacted] The diagnostic conducted to assess the proportionality of hazards for all the TTW analyses are reported in Appendix O.

The time to event analyses described in section 6.1.4.3.1. were tested in the scenario analysis (Table 20). Appendix O

Abbreviations: CDR-SB = Clinical dementia rating sum of boxes; KM= Kaplan-Meier; TTW = Time to worsening

Table 20 Summary of the TTW analysis results

Data	Method	HR (95% C.I.)	Applied as
18-month data			
Combined health state	[redacted]	[redacted]	**Base case**
Combined health states		[redacted]	Scenario
MCI due to AD	[redacted]	[redacted]	Scenario
Mild AD		[redacted]	
36 months and ADNI matched			
Combined health states	[redacted]	[redacted]	Scenario analysis
48 months data			
Combined health states	[redacted]	[redacted]	Scenario analysis

Abbreviations: AD = Alzheimer's disease; ADNI= Alzheimer's Disease Neuroimaging Initiative; C.I. = Confidence interval; TTW = Time to worsening.

8.1.2.1 Treatment discontinuation

The rate of all-cause discontinuation in Clarity AD in ApoE ε4 non carriers and heterozygotes was relatively constant in both the Core study and the OLE (Figure 19 and Figure 20).

For the Core study, the rate of discontinuation in the lecanemab arm was calculated to be 16.3% per year from the total number of discontinuation events (n=162) divided by the total cumulative exposure time to lecanemab (996.78 patient-years). This provided a monthly rate of all-cause discontinuation of 1.35% for lecanemab which is implemented in the model's base case. The value resulting from the OLE data (1.04%) was tested in the scenario analysis.

[redacted]

Abbreviations: AD = Alzheimer's disease; KM = Kaplan Meier; TTD = Time to discontinuation

8.1.3 Extrapolation of efficacy data

N/A

8.1.3.1 Extrapolation of [effect measure 1]

N/A

Table 21 Summary of assumptions associated with extrapolation of [effect measure]

Method/approach	Description/assumption
N/A	

8.1.4 Calculation of transition probabilities

8.1.4.1 AD progression

Data from Clarity AD is used to estimate the TPs during the first 18 months of the model time horizon for patients in the MCI due to AD and Mild AD health states.

The health state occupancy presented in Table 19 were assumed to have occurred within 18 months. These were adjusted for the model cycle length estimating monthly transition rates and transforming these back to probabilities, assuming a constant probability of the event occurring at each month and independence of events between months.

After 18 months, the treatment effect of lecanemab (HR: 0.739) is applied in the MCI due to AD, mild AD, and moderate AD health states. This may be considered a conservative approach, as it employs the copy increment method, not censoring patients after treatment discontinuation but instead imputing their efficacy based on the SoC arm.

Table 22 summarises disease progression transition included in the economic model. In the table, the sources for the TPs of institutionalisation and death are also shown for completeness, despite being described fully in section 8.2.

A complete overview of all the TPs included in the model, including both efficacy data from the clinical documentation and data from the published literature is provided in section 8.2.4.1. Clarity AD was conducted in different centres including Europe, and this data is considered relevant for the Danish population, as AD progression, is not expected to be subject to significant variation across different clinical settings.

Table 22 Transitions in the health economic model

Health state (from)	Health state (to)	Description of method	Reference
Before 18-month			
MCI due to AD, Mild AD Moderate AD and Severe AD	MCI due to AD Mild AD Moderate AD Severe AD	**Lecanemab and SoC**: Health state occupancy observed in Clarity AD at 18-month adjusted per model cycle length (1 month) (see Section 8.1.1)	Clarity AD
After 18-month			
MCI due to AD, Mild AD Moderate AD and Severe AD	MCI due to AD Mild AD Moderate AD Severe AD	**SoC**: Annual TPs derived from Potashman et al., 2021 adjusted per model cycle length (1 month) (see Section 8.2) **Lecanemab**: constant HR [0.739] applied to SoC arm TPs "forward"	Potashman et al., 2021 (65) and Clarity AD
Throughout time horizon			
Community setting	Institutionalised setting	Derived from severity specific risk of institutionalisation (see Section 8.2)	Knapp et al., 2016 (100)
Alive health states	Death	Derived from severity specific risk of 2023 death (see Section 8.2)	Crowell et al. 2023 (101)

Abbreviations: AD = Alzheimer's disease; MCI = mild cognitive impairment; SoC = Standard of Care; TPs = transition probabilities

Abbreviations: AD = Alzheimer's disease; MCI = mild cognitive impairment; SoC = Standard of Care

8.2 Presentation of efficacy data from published literature

8.2.1 Natural history

Natural history data derived from the literature (Potashman et al., 2021) (65), was used to inform natural disease progression.

Potashman et al., 2021 (65), was selected as the most appropriate source of natural history since the study included transitions on the complete AD spectrum, specific for Aβ+ patients. Furthermore, the disease stages defined in the model used by Potashman et al. 2021 (65) closely align with those in the current model, facilitating the use of these data. The progression rates reported in the publication were estimated through 6 stages: asymptomatic, MCI due to AD, Mild AD, Moderate AD, Severe AD, and death (Table 23). 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.

Table 23 Annual TPs (as %) reported in Potashman et al., 2021 (65)

From ↓ to →	Asymptomatic	MCI due to AD	Mild AD	Moderate AD	Severe AD
Asymptomatic	59.2%	40.8%	0.0%	0.0%	0.0%
MCI due to AD	5.3%	68.2%	15.9%	5.7%	0.2%
Mild AD	0.0%	3.0%	51.8%	31.6%	4.3%
Moderate AD	0.0%	0.0%	1.8%	38.4%	28.6%
Severe AD	0.0%	0.0%	0.0%	1.3%	52.0%

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

Sources: Potashman et al. 2021 (65)

For inclusion in the economic model, data were adjusted by adding the transition to the asymptomatic state to the probabilities of remaining or transitioning to MCI due to AD and removing death, then reweighting the remaining distributions. The resulting annual probabilities are shown in Table 24. The monthly TPs applied in the economic model for natural history disease progression are summarised in section 8.2.4.1.

Table 24 Annual TPs (as %) adapted from Potashman et al., 2021 (65) and included in the economic model (SoC after 18 months)

From ↓ to →	MCI due to AD	Mild AD	Moderate AD	Severe AD
MCI due to AD	77.1%	16.7%	6.0%	0.2%
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; SoC = Standard of care
Sources: Potashman et al. 2021 (65)

8.2.2 Mortality

Mortality data from Clarity AD was immature, as only 0.8% of the overall ITT-FAS+ population died during the study, and it was considered too uncertain to inform long-term predictions in the economic analysis. Therefore, AD specific mortality was sourced from the literature. Crowell et al., 2023 (101) reported HRs of death across all stages of AD compared with cognitively normal participants, using Cox proportional-hazards models adjusting for age, sex, and other variables (102). 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. 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 (101). Relative risks from 'model 2' reported by Crowell et al., 2023 (101) 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. A scenario was conducted to test the impact of assuming the mortality HR for patients in MCI due to AD is equal to the general population. The relative effect of mortality was applied to the age- and sex-adjusted estimates of general population mortality, using Danish life tables in accordance with DMC guidelines (103). Mortality is applied as the sex-weighted annual mortality adjusted to the monthly cycle length.

Table 25 Mortality HR by health state

From ↓ to →	HR (95% CI)
MCI due to AD	0.63 (0.46, 0.88)
Mild AD	2.43 (1.81, 3.26)
Moderate AD	3.77 (2.66, 5.34)
Severe AD	8.53 (5.45, 13.3)

Abbreviations: AD = Alzheimer's disease; CI= Confidence interval; HR = hazard ratio; MCI = mild cognitive impairment.
Source: Crowell et al., 2023 (101)

8.2.3 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 focused on identifying TPs between health states based on disease severity rather than care setting. All four studies that reported a risk of institutionalisation were US-based, and none reported institutionalisation in an Aβ positive population (104-107).

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 specific for the Danish setting. Therefore, two sources that reported institutionalisation rates in patients with AD in other European countries were considered. Knapp et al., 2016 (100) is a patient registry analysis of 3075 United Kingdom (UK)-based individuals with AD, and Belger et al., 2019 (GERAS study) (67) is a prospective, non-interventional cohort study in patients with AD in three European countries (France, Germany, and UK), comprising 1495 patients.

Knapp et al., 2016 (100) was selected for the base case analysis since the authors report the risk of institutionalisation based on a larger sample population than Belger et al., 2019 (67), and was therefore considered to be more reliable. The study reports six-month probabilities of admission to an institution whilst in mild AD, moderate AD, and severe AD. These were converted to monthly probabilities to align with model cycle length. The probability of transitioning to institutionalised care increases with increasing severity of disease (100). In the absence of data reported by Knapp et al., 2016 (100), individuals in the MCI due to AD health state are assumed to have no risk of institutionalisation. The associated risk of institutionalisation for patients in mild AD is also very low (0.51%), supporting the assumption of 0% institutionalisation risk for MCI due to AD patients. This aligns with the consensus among experts at the Nordic health technology assessment (HTA) advisory board (November 2023) on the fact that patients with MCI due to AD are not expected to be institutionalised in Denmark (108).

Belger et al., 2019 (67) was tested in the scenario analysis. The study reports three-year probabilities of admission to an institution while in mild AD, moderate AD, and Severe AD, which were converted to monthly probabilities to align with the model cycle length. Similar to Knapp et al., 2016 (100), it was assumed that patients MCI due to AD have 0% chance of hospitalisation. The probability of transitioning to institutionalised care increases with increasing severity of disease, consistent with Knapp et al., 2016 (100). The monthly TPs applied in the economic model for institutionalisation are summarised in section 8.2.4.1.

Table 26 Probabilities of institutionalisation due to AD from Knapp et al., 2016 & Belger et al., 2019

Model health state	Knapp et al., 2016	Belger et al., 2019
	6-month probability	3-year probability
MCI due to AD	0%	0%
Mild AD	3.00%	15.6%
Moderate AD	8.00%	29.5%
Severe AD	10.00%	32.5%

Source: Adapted from Knapp et al., 2016 (100) and Belger et al, 2019 (67).
Abbreviations: AD = Alzheimer's disease; MCI = Mild cognitive disorder

8.2.4 Calculation of transition probabilities

The TPs from both Clarity AD and the literature were adjusted for the model cycle length estimating monthly transition rates and transforming these back to probabilities, assuming a constant probability of the event occurring at each month and independence of events between months. The monthly TPs used in the economic model are summarised in section 8.2.4.1.

8.2.4.1 Overview of the TPs included in the model

The following paragraphs provide a summary the data included in the economic model and described throughout Section 8.

AD progression

Table 27 provides an overview of the monthly TPs for AD progression used in the model. Note that the assumptions on AD progression taken following lecanemab discontinuation are described in section 8.4.

Table 27 Monthly TPs (reported in %) for disease progression

From ↓ to →	MCI due to AD	Mild AD	Moderate AD	Severe AD
First 18 months				
SoC				
MCI due to AD [a]	[redacted]	[redacted]	[redacted]	[redacted]
Mild AD [a]	[redacted]	[redacted]	[redacted]	[redacted]
Moderate AD [b]	0.00%	0.22%	Residuals	4.38%
Severe AD [b]	0.00%	0.00%	0.21%	Residuals
Lecanemab				
MCI due to AD [a]	[redacted]	[redacted]	[redacted]	[redacted]
Mild AD [a]	[redacted]	[redacted]	[redacted]	[redacted]
Moderate AD [c]	0.00%	0.22%	Residuals	3.25%
Severe AD [c]	0.00%	0.00%	0.21%	Residuals
After 18 months				
SoC [b]				
MCI due to AD	Residuals	1.51%	0.51%	0.02%
Mild AD	0.28%	Residuals	3.51%	0.40%
Moderate AD	0.00%	0.22%	Residuals	4.38%
Severe AD	0.00%	0.00%	0.21%	Residuals
Lecanemab [c]				
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]

Sources: a: Clarity AD (68), b: Potashman et al. 2021 (65) c: Potashman et al., 2021 with treatment effect applied as TTW HR

Abbreviations: AD = Alzheimer's disease; MCI = Mild cognitive disorder; SoC = Standard of Care

Mortality

The HR included in Table 25 are applied to the mortality of the Danish population throughout the time horizon.

Institutionalisation

The 6-month probabilities by health state from Knapp et al., 2016 were transformed into monthly transition rates and back to probabilities, assuming a constant probability of the event occurring at each month and independence of events between months.

Table 28 Institutionalisation probabilities included in the model

Health state	Monthly probability of institutionalisation (%)	
	Knapp et al., 2016 (base case)	Belger et al., 2019 (scenario)
MCI due to AD	0%	0.00%
Mild AD	0.51%	0.43%
Moderate AD	1.38%	0.82%
Severe AD	1.74%	0.90%

Source: Knapp et al., 2016 (100)
Abbreviations: AD = Alzheimer's disease; MCI = Mild cognitive disorder

8.3 Modelling effects of subsequent treatments

Not applicable

8.4 Other assumptions regarding efficacy in the model

Clarity AD did not include treatment stopping criteria for lecanemab. The SmPC for lecanemab (1) states that treatment with lecanemab should be discontinued once the patient progresses to moderate AD and clinical experts have suggested other alternative situations in which patients could discontinue treatment. Patients might discontinue treatment with lecanemab in the following circumstances:

- Based on entry to the Moderate or Severe AD health states:
    - As lecanemab is indicated for patients with MCI due to AD and Mild AD, stopping treatment at Moderate AD and Severe AD is warranted
    - Clinical experts stated that it may be considered unethical to continue a treatment despite the worsening of the disease, and many patients would want the benefits of the treatment at MCI due to AD or Mild AD, but not at Moderate AD or Severe AD
- Based on entering institutionalised care
    - It was considered unlikely to continue treatment in institutionalised patients, as institutionalisation often correlates with poor general conditions, regardless of the AD stage

In the economic model, patients are assumed to stop treatment upon entering Moderate or Severe AD states and entering institutionalisation.

Continued treatment with lecanemab is expected to be ideal for early AD patients, as suggested by the Clarity AD OLE study results (82). Nevertheless, a time-based stopping criteria was also mentioned as a possible approach taken in clinical practice , where it has been suggested by clinical experts and observed in other modelling studies (109). Stopping treatment at 2 years (in addition to the treatment stopping criteria described above) was therefore tested in the scenario analysis.

8.4.1 Durability of lecanemab effect after discontinuation

In the Clarity AD study, subjects that discontinued treatment at any time were required to complete a single follow up visit after 3 months. Therefore, there are no data available from the study to inform the long-term durability of the lecanemab treatment effect after discontinuation.

However, a residual treatment effect is expected based on the mechanism of action of lecanemab as it takes time for patients' toxic amyloid (protofibril and plaque) levels to reaccumulate once cleared (at a reaccumulation rate of 2.6 CL/year following lecanemab treatment). The published literature also indicates that patients with amyloid PET levels below 50 CL show little to no clinical progression within the subsequent 3.4 to 4.5 years (110). Based on 2.6 CL/year reaccumulation, it is estimated that patients who have received at least 18 months of lecanemab treatment can remain below 50 CL for approximately 11 years following lecanemab treatment.

In the economic model, patients discontinued treatment due to all-cause discontinuation, due to progression to moderate/severe disease, institutionalisation, or time-based stopping.

All-cause discontinuation

The base-case analysis explores a potential dilution of treatment effect due to all-cause discontinuation using the copy-increments approach to missing data (see Appendix K.2.1). This approach may be considered conservative as placebo values are used to impute missing values in the lecanemab group.

Discontinuation at moderate / severe disease (as per SmPC)

The economic model predicts a mean time in Moderate AD of 1.17 years with lecanemab, before progression to Severe AD. Therefore, most patients treated with lecanemab until moderate AD are not expected to reaccumulate amyloid back to 50 CL prior to disease progression. To explore a possible dilution of treatment effect after discontinuation at moderate or severe AD, a 25% reduction in treatment effect was applied to the moderate AD to severe AD TTW-HR in the base case analysis. A scenario is presented with no reduction in treatment effect.

Discontinuation at institutionalisation

Treatment effect is maintained after institutionalisation in mild AD, as initiation of institutional care could be unrelated to a 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. This assumption is not considered to have a relevant impact on the model, as it affects a limited number of patients.

[redacted]

8.5 Overview of modelled average treatment length and time in model health state

Treatment length is estimated in the model using TTD KM data from the Clarity AD Core study extrapolated using a constant rate of discontinuation (see section 8.1.2.1).

Table 29 Estimates in the model

	Modelled average TTD *	Modelled median TTD *	Observed median from Clarity AD
Lecanemab	[redacted]	[redacted]	[redacted]
SoC	N/A	N/A	N/A

Abbreviations: TTD, Time to discontinuation.
Notes: * Modelled average and median TTD is reported in the economic model in sheet "Tables for submission" cells C6 and D6

In Table 30, the modelled average treatment length and time in model health state are reported in months. The key assumptions used to derive these estimates are derived from the estimated model TPs and the assumptions on lecanemab discontinuation included in the base case.

Table 30 Overview of modelled average treatment length and time in model health state, undiscounted and not adjusted for half cycle correction (months)

Treatment	Treatment length	MCI due to AD	Mild AD	Moderate AD	Severe AD
Lecanemab	[redacted]	[redacted]	[redacted]		[redacted]
SoC	[redacted]	[redacted]	[redacted]		[redacted]

Abbreviations: AD = Alzheimer's disease; MCI = Mild cognitive disorder; SoC = standard of care

9. Safety

9.1 Safety data from the clinical documentation

The safety data presented in the following section is for the subgroup of patients who are ApoE ε4 non-carriers and heterozygotes in the safety analysis set from the Clarity AD Core Study (September 13th 2022 data cut-off) and is based on the safety analysis set which is comprised of all allocated patients who received at least one dose of study drug (68).

For the Clarity AD OLE Study, the safety data presented in the following section is for the subgroup of patients who are ApoE ε4 non-carriers and heterozygotes in the safety analysis set from the Clarity AD OLE study, which consists of all subjects who received lecanemab in the Core Study and all subjects who received placebo in the Core Study and received lecanemab in the OLE study (82).

An overview of the safety events in both the Clarity AD Core Study and OLE Study is presented in Table 31 below.

Table 31 Overview of safety events (September 13th 2022 data cut-off)

	Clarity AD Core Study		Clarity AD OLE Study
Take yo	Lecanemab N = 757	Placebo N = 764	Lecanemab (Core + OLE) N = 1366
Number of adverse events, n	NR	NR	NR

	Clarity AD Core Study		Clarity AD OLE Study
Take yo	Lecanemab N = 757	Placebo N = 764	Lecanemab (Core + OLE) N = 1366
Number and proportion of patients with ≥1 adverse events, n (%)	667 (88.1)	620 (81.2)	[redacted]
Number of serious adverse events, n	NR	NR	[redacted]
Number and proportion of patients with ≥ 1 serious adverse events, n (%)	112 (14.8)	86 (11.3)	[redacted]
Number of CTCAE grade ≥ 3 events, n	NR	NR	[redacted]
Number and proportion of patients with ≥ 1 CTCAE grade ≥ 3 events, n (%)	NR	NR	[redacted]
Number of adverse reactions, n	NR	NR	[redacted]
Number and proportion of patients with ≥ 1 adverse reactions, n (%)	314 (41.5)	147 (19.2)	[redacted]
Number and proportion of patients who had a dose reduction, n (%)	NR	NR	NR
Number and proportion of patients who discontinue treatment regardless of reason, n (%)	[redacted]	[redacted]	[redacted]
Number and proportion of patients who discontinue treatment due to adverse events, n (%)	[redacted]	[redacted]	[redacted]

Source: Core Study = Eisai DOF (Table 14.3.1.2.1; Table 14.3.1.2.2) (83); OLE Study = Eisai DOF (Table 14.3.1.2.1nh) (111), Eisai DOF (Table 14.1.1.4.1nh) (86)
*Note: Based on the OLE Treated Set (n = 1187) which includes Core 10 mg/kg biweekly subjects are those assigned to lecanemab (10 mg/kg biweekly) in Core Study, and newly treated Core placebo subjects are those assigned to placebo in Core Study.

An overview of the serious adverse events occurring in more than 2 patients in both the Clarity AD Core Study and OLE Study is presented in Table 32 below.

Table 32 Serious adverse events occurring in ≥ 5% of patients; MedDRA Preferred Item

	Clarity AD Core Study		Clarity AD OLE Study
Adverse events	Lecanemab n=757	Placebo n=764	Lecanemab (Core + OLE) n=1366
	Number of patients with adverse events	Number of patients with adverse events	Number of patients with adverse events
Adverse event, n (%)	112 (14.8)	86 (11.3)	278 (20.4)

Abbreviations: OLE = open label extension

Adverse events used in the health economic model

Criteria for selecting adverse events for inclusion in the cost-effectiveness analysis were as follows:

- ARIA-E, ARIA-H, and infusion-related reactions (IRR) were included irrespective of incidence and severity given these are AEs of special interest (AESIs)
- All other events were assessed based on the rule of ≥5% treatment-related incidence in either treatment arm of Clarity AD, as typically applied in HTA; Nevertheless,

the incidence of all treatment-related AEs (TRAEs) other than AESIs was <5% in either arm, therefore the only AEs included in the cost-effectiveness analysis were ARIA-E, ARIA-H and infusion-related reactions.

AE rates were modelled based on maximum radiographic severity for ARIA events and based on NCI-CTCAE criteria for infusion related reactions. ARIA events were separated by the presence of symptoms to reflect the significant differences in QoL, costs, and monitoring differences between symptomatic and asymptomatic ARIA events. ARIA-H can occur concurrently with ARIA-E (concurrent ARIA-H with ARIA-E) or alone (isolated ARIA-H). Rates of isolated ARIA-H were used to avoid double-counting given concurrent ARIA-H with ARIA-E was counted under ARIA-E and treatment-emergent rates were used given the natural nature of ARIA-H occurrence for AD. The rate of IRR for SoC was assumed to be 0% given these patients will not receive a placebo infusion in clinical practice. One symptomatic ARIA-E event had no severity classification reported; the event was assumed to be mild as most ARIA-E events which occurred in Clarity AD were mild.

Table 33 Adverse events used in the health economic model

Adverse events	Intervention	Comparator		
IRR, n (%)			Eisai, Clarity AD CSR (Tables 14.3.2.4, 13.3.2.6.10.6. and 14.3.2.6.14). (60)	Treatment related incidence of grade 3+ AE occurring in 5% of patients in either treatment arm of Clarity AD and IRR) and ARIA regardless of their incidence or severity
Grade 1	[redacted]	[redacted]		
Grade 2	[redacted]	[redacted]		
Grade 3	[redacted]	[redacted]		
Grade 4	[redacted]	[redacted]		
ARIA-E asymptomatic				
Mild	[redacted]	[redacted]		
Moderate	[redacted]	[redacted]		
Severe	[redacted]	[redacted]		
ARIA-E symptomatic				
Mild	[redacted]	[redacted]		
Moderate	[redacted]	[redacted]		
Severe	[redacted]	[redacted]		
ARIA-H asymptomatic				
Mild	[redacted]	[redacted]		
Moderate	[redacted]	[redacted]		
Severe	[redacted]	[redacted]		
ARIA-H symptomatic				
Mild	[redacted]	[redacted]		
Moderate	[redacted]	[redacted]		
Severe	[redacted]	[redacted]		

Abbreviations: AE = Adverse event; ARIA-E = amyloid-related imaging abnormality-oedema/effusion; ARIA-H = amyloid-related imaging abnormality-microhaemorrhage and haemosiderin deposit; IRR = Infusion related reaction

*ARIA-E and ARIA-H based on maximum radiographic severity level. For ARIA-H radiographical severity is defined by total number of new microhaemorrhages for microhaemorrhage (mild: =<4, moderate: 5-9, severe:>=10), total number of areas for superficial siderosis (mild:1, moderate:2, severe:>2), and severity by investigator in AE CRF for macrohaemorrhage. If a subject had two or more ARIAs with different severities, then the event with the maximum severity was used for that IRR are based on National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE: mild= grade 1, Moderate= grade 2, severe= grade 3, serious= grade 4)

9.2 Safety data from external literature applied in the health economic model

N/A

10. Documentation of health-related quality of life (HRQoL)

HRQoL in the economic model is based on EQ-5D-5L from Clarity AD integrated with data from the literature. The other HRQoL measurement collected in Clarity AD are reported in Appendix KK.4.3.

Table 34 Overview of included HRQoL instruments

Measuring instrument	Source	Utilization
EQ-5D-5L	Clarity AD	Health state utilities and disutilities

10.1 Presentation of the health-related quality of life [EQ-5D-5L Health today]

10.1.1 Study design and measuring instrument

In Clarity AD, the EQ-5D-5L index and EQ-5D VAS was collected for patients, patients by study partner and study partner. The study design follows the clinical trial Clarity AD, and the a priori expectation in the changes in HRQoL is that the patients on lecanemab have a lower rate of deterioration in HRQoL than the SoC group, in all three measures used (i.e., patient-reported, partner as a proxy, and results from the partners).

EQ-5D-5L is widely accepted as the standard measure for evaluating patients' QoL. Its validity, reliability, and sensitivity have been studied and widely accepted (112).

The EQ-5D-5L questionnaire was used in the manner it is validated for. There is no reason to believe that the study design or the EQ-5D-5L questionnaire would cause a risk of bias.

EQ-5D health today was analysed with a longitudinal model [mix model repeated measures (MMRM)] and reported in sections 10.1.1 and 10.1.2, while the EQ-5D-5L index score was analysed by health state and leveraged in the economic analysis (section 10.2).

10.1.2 Data collection

The HRQoL data was collected in conjunction with the Clarity AD trial from the patients and their partner, every 6 months, with a total follow-up of 18 months. A total of 1466 subjects were included in the ITT FAS+ ApoE ε4 non-carrier or heterozygote population, 1419 (97%) of which were included in the HRQoL analysis.

At the item level, missing responses were managed as per the scoring manual. For the EQ-5D-5L, missing data were not imputed or replaced. For the longitudinal modelling, missing data were handled under the missing-at-random (MAR) assumption in the MMRM model.

The pattern of missing data and completion from the EQ-5D Health today over time is demonstrated in Table 35 for patients' data, in Table 36 for patients' by proxy and Table 37 for study partners.

10.1.2.1 Patient reported

Table 35 Pattern of missing data and completion (Patient EQ-5D-Health today)

Time point	HRQoL population N	Missing N (%)	Expected to complete N	Completion N (%)
Baseline	[redacted]	[redacted]	[redacted]	[redacted]
6 months	[redacted]	[redacted]	[redacted]	[redacted]
12 months	[redacted]	[redacted]	[redacted]	[redacted]
18 months	[redacted]	[redacted]	[redacted]	[redacted]

Source: CLARITY AD (68)

Abbreviations: EQ-5D-5L = European QoL – 5 Dimensions – 5 Levels; HRQoL = Health Related Quality of Life; N/A = Not available

10.1.2.2 Partner as a proxy

Table 36 Pattern of missing data and completion (Patient by Study partner EQ-5D-Health today)

Time point	HRQoL population N	Missing N (%)	Expected to complete N	Completion N (%)
Baseline	[redacted]	[redacted]	[redacted]	[redacted]
6 months	[redacted]	[redacted]	[redacted]	[redacted]
12 months	[redacted]	[redacted]	[redacted]	[redacted]
18 months	[redacted]	[redacted]	[redacted]	[redacted]

Source: CLARITY AD (68)

Abbreviations: EQ-5D-5L = European QoL – 5 Dimensions – 5 Levels; HRQoL = Health Related Quality of Life; N/A = Not available

10.1.2.3 Partner results

Table 37 Pattern of missing data and completion (Study partner EQ-5D-Health Today)

Time point	HRQoL population N	Missing N (%)	Expected to complete N	Completion N (%)
Baseline	[redacted]	[redacted]	[redacted]	[redacted]
6 months	[redacted]	[redacted]	[redacted]	[redacted]
12 months	[redacted]	[redacted]	[redacted]	[redacted]
18 months	[redacted]	[redacted]	[redacted]	[redacted]

Source: CLARITY AD (68)

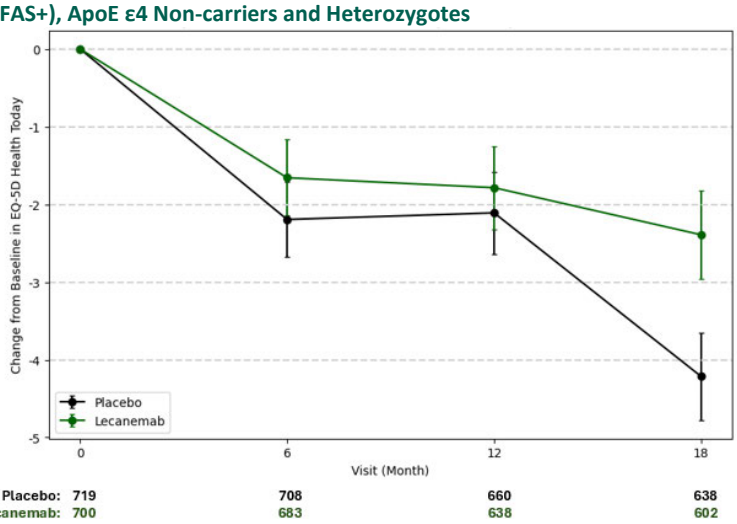
Abbreviations: EQ-5D-5L = European QoL – 5 Dimensions – 5 Levels; HRQoL = Health Related Quality of Life; N/A = Not available

10.1.3 HRQoL results

10.1.3.1 Patient reported

The analysis showed an increased mean difference in EQ-5D Health Today across the trial follow-up, which result in a statically significant difference at 18 months.

Figure 23 Change in Patient-Reported EQ-5D Health Today Score up to 18 Months from Baseline; Clarity AD (FAS+), ApoE ε4 Non-carriers and Heterozygotes



Source: CLARITY AD (68)

Abbreviations: AD = Alzheimer's Disease; ApoE ε4 = Apolipoprotein E4; EQ-5D-5L = European QoL – 5 Dimensions – 5 Levels; SE = Standard Error

Table 38 HRQoL Change in patient reported EQ-5D-5L summary statistics

	Lecanemab		SoC		Intervention vs. comparator
	N	Mean (SE)	N	Mean (SE)	Difference (95% CI) p-value
Baseline					
6 months					
12 months					
18 months					

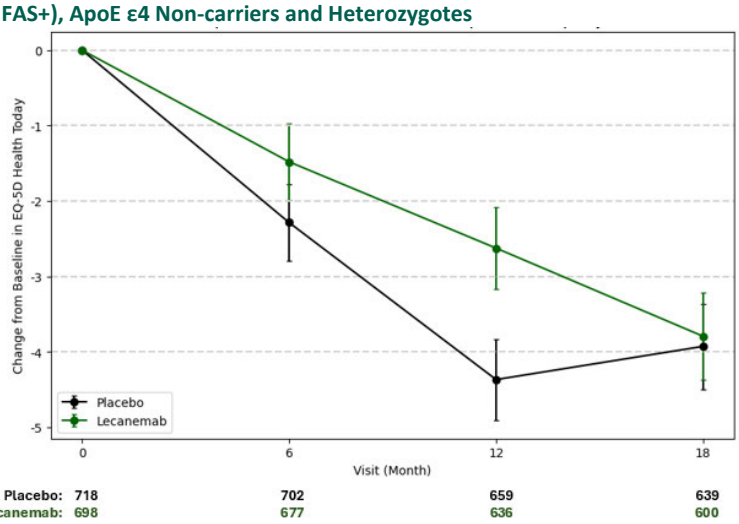
Source: CLARITY AD (68)

Abbreviations: HRQoL = Health Related Quality of Life; EQ-5D-5L = European QoL – 5 Dimensions – 5 Levels; SoC = Standard of Care; SE = Standard Error; CI = Confidence Interval

10.1.3.2 Partner as a proxy

The results showed an increase in separation from baseline to 12 months, although this was reduced at 18 months.

Figure 24 Change in Partner proxy EQ-5D Health Today Score up to 18 Months from Baseline; Clarity AD (FAS+), ApoE ε4 Non-carriers and Heterozygotes



Source: CLARITY AD (68)

Abbreviations: AD = Alzheimer's Disease; ApoE ε4 = Apolipoprotein E4; EQ-5D-5L = European QoL – 5 Dimensions – 5 Levels; SE = Standard Error

Table 39 HRQoL Change in partner proxy EQ-5D-5L summary statistics

	Lecanemab		SoC		Intervention vs. comparator
	N	Mean (SE)	N	Mean (SE)	Difference (95% CI) p-value
Baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
6 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
12 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
18 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

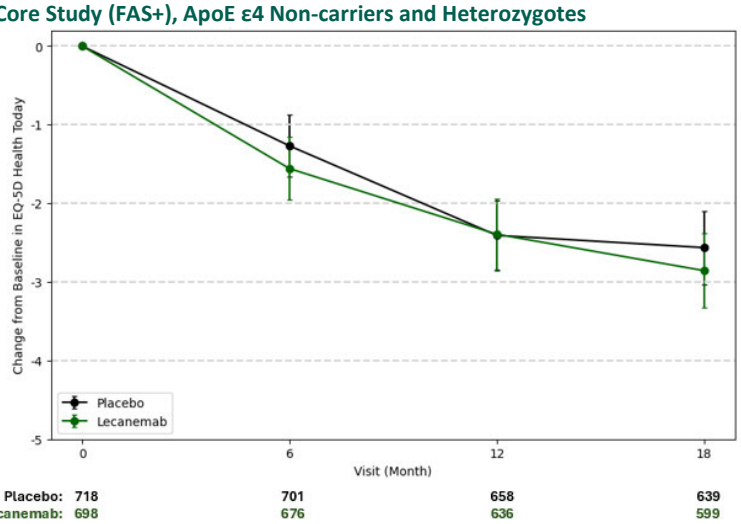
Source: CLARITY AD (68)

Abbreviations: HRQoL = Health Related Quality of Life; EQ-5D-5L = European QoL – 5 Dimensions – 5 Levels; SoC = Standard of Care; SE = Standard Error; CI = Confidence Interval

10.1.3.3 Partner results

Of particular interest are the results for study partner, showing a clear decline in HRQoL at each time point, in both treatment arms.

Figure 25 Change in Partner-Reported EQ-5D Health Today Score up to 18 Months from Baseline; Clarity AD Core Study (FAS+), ApoE ε4 Non-carriers and Heterozygotes



Source: CLARITY AD (68)

Abbreviations: AD = Alzheimer's Disease; ApoE ε4 = Apolipoprotein E4; EQ-5D-5L = European QoL – 5 Dimensions – 5 Levels; SE = Standard Error

Table 40 HRQoL Change in patient reported EQ-5D-5L summary statistics

	Lecanemab		SoC		Intervention vs. comparator
	N	Mean (SE)	N	Mean (SE)	Difference (95% CI) p-value
Baseline					
6 months					
12 months					
18 months					

Source: CLARITY AD (68)

Abbreviations: HRQoL = Health Related Quality of Life; EQ-5D-5L = European QoL – 5 Dimensions – 5 Levels; SoC = Standard of Care; SE = Standard Error; CI = Confidence Interval

10.2 Health state utility values (HSUVs) used in the health economic model

In the economic model, data from Clarity AD described in section 10.2.1 are integrated with values from the literature described in section 10.3. The complete overview of the utility and disutility values applied in the model is provided in Table 43.

10.2.1 HSUV calculation

Utilities are age-adjusted in the economic model following DMC recommendations. The adjustment is applied in the economic model to the values summarised in Table 43. Table 41 shows the resulting health state mean utilities and SD, calculated with Danish EQ-5D tariffs (113). Differences between study arms observed in MCI and Mild AD may reflect lecanemab HRQoL benefit, independent of disease progression. The values from Moderate and Severe AD states should be considered with caution, given the limited number of observations. It is worth noting that, across arms, self-reported values were

higher than the one reported by caregivers as proxy, and that the discrepancy is larger in more advanced stages of the disease.

Table 41 Clarity AD EQ-5D-5L data by health state (CDR-SB)

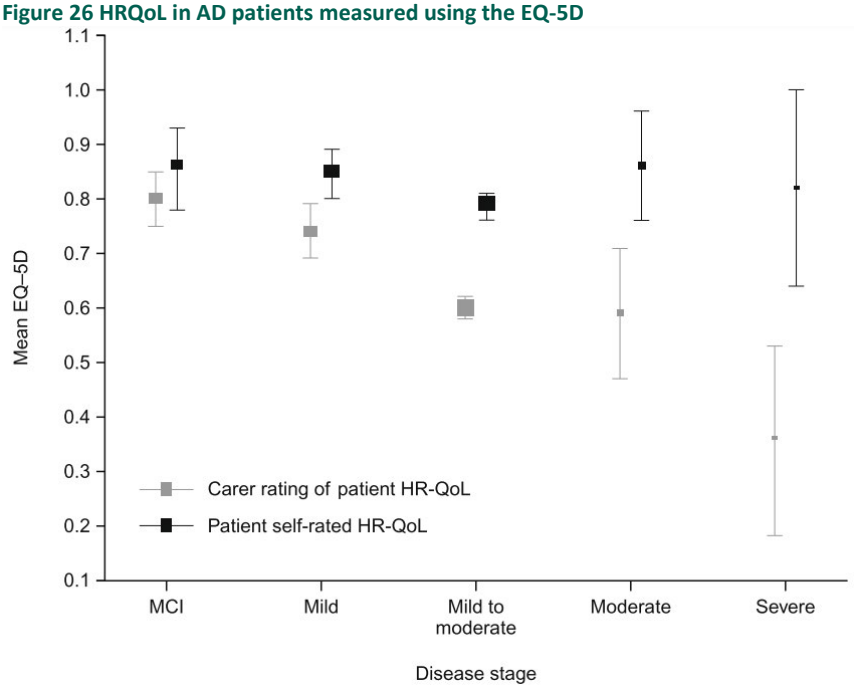
	Patient			Caregiver as proxy		
	Lecanemab (N=723)	SoC (N=743)	Combined	Lecanemab (N=723)	SoC (N=743)	Combined
MCI due to AD (n)	1836	1769	3605	1826	1762	3588
Mean (C.I.)	0.931 (0.927, 0.936)	0.922 (0.917, 0.927)	0.927 (0.923, 0.930)	0.908 (0.902, 0.913)	0.901 (0.895, 0.907)	0.904 (0.900, 0.908)
Mild AD (n)	740	889	1629	740	887	1627
Mean (C.I)	0.930 (0.922, 0.939)	0.922 (0.915, 0.929)	0.926 (0.920, 0.931)	0.865 (0.855, 0.875)	0.838 (0.827, 0.849)	0.850 (0.842, 0.858)
Moderate AD (n)	42	67	109	43	67	110
Mean (C.I.)	0.846 (0.769, 0.923)	0.916 (0.894, 0.938)	0.889 (0.856, 0.922)	0.726 (0.658, 0.793)	0.750 (0.701, 0.799)	0.741 (0.701, 0.780)
Severe AD (n)	0	4	4	0	5	5
Mean (C.I.)	-	0.659 (0.250, 1.067)	0.659 (0.250, 1.067)	-	0.333 (-0.400, 1.067)	0.333 (-0.400, 1.0670.5909)

Source: Clarity AD (114)

Abbreviation: AD = Alzheimer's disease; C.I. = Confidence Interval; MCI = Mild Cognitive Impairment, N = Number of patients in each treatment arm; n = Number of patients in each health-state, per treatment arm; SoC = standard of care.

These findings are consistent with the recent literature: an SLR and meta-analysis including EQ-5D estimates from 58 studies highlighted that for patients in MCI, there was no statistically significant difference in self-rated and proxy rated values in the MCI state, but this difference increased and became significant beyond the MCI stage (75).

Figure 26 HRQoL in AD patients measured using the EQ-5D



Source: Landeiro et al., 2020 (75)
Abbreviations: AD = Alzheimer's disease; EQ-5D = EuroQol-5 Dimension; HRQoL = Health-related quality of life

The reason for this discrepancy is multifaceted and might include the patients' adaptation to their long-term condition, the increasing pressure caregivers experience as dementia symptoms worsen, and the lack of a specific EQ-5D cognitive domain, hindering the detection of differences between Mild, Moderate and Severe AD stages (75). The limitation of patient self-awareness in severe cognitive impairment was also cited as a possible explanation (75). The limitations of the EQ-5D instrument and the low reliability of patient reported values in the most advanced stages were also highlighted in the published literature (115).

Therefore, in the economic model, patient-reported data were used for MCI due to AD and Mild AD, while proxy-reported data from the literature were used for Moderate AD and Severe AD health states (Table 43). Specifically, the same decrement observed between Mild AD and Moderate AD and between Moderate AD and Severe AD were applied to the Mild AD values from Clarity to estimate the Moderate AD and Severe AD states (see calculations in Table 43). Landeiro et al., 2020 (75) is further reported in section 10.3, as outlined in this DMC template.

10.2.1.1 Mapping

N/A

10.2.2 Disutility calculation

Disutilities associated with adverse events were not applied in the model to avoid double-counting, as these are considered inherently captured in the trial utility data. After DMC request received on May 20, 2025, a scenario was included accounting for disutility of adverse events (IRR and ARIA events).

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(77) and Sullivan et al., 2006(78), respectively. 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(76). 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 assumptions aligned with the current Lecanemab submission for NICE. 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.

Table 42 Disutility leveraged in scenario requested by DMC on May 20, 2025

	Disutility	Duration (Days)	Source
IRR			
Mild	0	N/A	Assumption
Moderate	0	N/A	Assumption
Severe	0.01	0.125	Boye et al., 2011
Serious	0.01	0.125	Boye et al., 2011
ARIA-E			
Mild	0	N/A	Assumption
Moderate	0	N/A	Assumption
Severe	0.0266	6	Sullivan et al., 2006
Serious	0.0266	6	Sullivan et al., 2006
Isolated ARIA-H			
Mild	0	N/A	Assumption
Moderate	0	N/A	Assumption
Severe	0.1	6	Meckley et al., 2010
Serious	0.1	6	Meckley et al., 2010

Source: Boye et al., 2011 (76), Meckley et al., 2010 (77), Sullivan et al., 2006 (78).
Abbreviation: IRR = Infusion related reactions, MCI = Mild Cognitive Impairment.

Values from the literature were used to inform utilities in institutionalisation as Clarity AD did not include information on setting of care, these were also not reported by Landeiro et al., 2020 (75).

Utilities for institution were derived by applying a utility decrement to the community setting utilities. The utility decrement was sourced from Farina et al., 2020 (74) which reported on disparities in patient utilities between community and institutional care. Using a regression model, the study estimated the effect of institutionalisation, specifically residential home care settings, on EQ-5D-3L. The findings indicated a significant association between residing in a care home and diminished EQ-5D-3L reported by proxy [unstandardised B coefficient -0.13 (95% C.I: -0.23, -0.03)] and no decrement in EQ-5D-3L self-reported [unstandardised B coefficient 0.00; (95% C.I: -0.12, 0.11)]. These were applied in the model in alignment with the data from Clarity AD (self -reported values for MCI due to AD and Mild AD, by proxy for Moderate AD and Severe AD health states). Farina et al., 2020 (74) is further reported in section 10.3, as outlined in this DMC template.

10.2.3 HSUV results

Table 43 describes the utility and disutility values applied in the model. The impact of the utilities are explored within both the DSA and PSA. In addition, in the scenario analysis, the use of Farina et al., 2020 (74) is tested to estimate the utility values for Moderate AD and Severe AD.

Table 43 Overview of health state utility values [and disutilities]

	Results [95% CI]	Instrument	Tariff (value set) used	Comments
Lecanemab				
MCI due to AD	[redacted]	EQ-5D-5L	DK	Clarity AD patient reported
Mild AD	[redacted]	EQ-5D-5L	DK	Clarity AD patient reported
Moderate AD	[redacted]	EQ-5D-5L	DK and literature value where tariff is not specified	Difference between Mild AD and Moderate AD proxy reported utility values in Landeiro et al., 2020 (75) applied to Mild AD utility value for Mild AD from Clarity AD. Note that in Landeiro et al., 2020 (75) tariffs and type of EQ-5D questionnaire are not specified (3L or 5L) $0.931^{a} - (0.740^{b} - 0.590^{b}) = 0.780$ Scenario analysis using Farina et. al., 2020 (74): $0.931^{a} - (0.70^{c} - 0.50^{c}) = 0.730$
Severe AD	[redacted]	EQ-5D-5L	DK and literature value where tariff is not specified	Difference between Moderate AD and Severe AD proxy reported utility values in Landeiro et al., 2020 (75) applied to Moderate AD utility value Note that in Landeiro et al., 2020 (75) tariffs and type of EQ-5D questionnaire are not specified (3L or 5L) $0.780 - (0.590^{b} - 0.360^{b}) = 0.550$ Scenario analysis using Farina et. al., 2020 (74): $0.730 - (0.50^{c} - 0.40^{c}) = 0.550$
SoC				

MCI due to AD	[redacted]	EQ-5D-5L	DK	Clarity AD patient reported
Mild AD	[redacted]	EQ-5D-5L	DK	Clarity AD patient reported
Moderate AD	[redacted]	EQ-5D-5L	DK and literature value where tariff is not specified	Same method applied for the lecanemab arm
Severe AD	[redacted]	EQ-5D-5L	DK and literature value where tariff is not specified	Same method applied for the lecanemab arm
Disutilities				
Institution				
Moderate AD and Severe AD	-0.13	EQ-5D-3L	UK	Disutility value associated to institutionalisation (proxy reported) from Farina et al., 2020 (74)

Source: a = Clarity AD (68) ; b = Landeiro et al., 2020 (75), ; c = Farina et al., 2020 (74)
Abbreviation: AD =Alzheimer's disease; MCI =Mild Cognitive Impairment
Notes: * in the sensitivity analysis, the values used to derive the health states utilities for Moderate and Severe AD are directly varied.

10.3 Health state utility values measured in other trials than the clinical trials forming the basis for relative efficacy

Two studies were used to inform the utility values included in the model, Landeiro et al., 2020 (75) and Farina et al., 2020 (74). Farina et al.,2020 (74) was identified through the SLR conducted on utility values, while Landeiro et al., 2020 (75) is a systematic literature review and meta-analysis and was identified by hand search.

10.3.1 Study design (Farina et al 2020)(74)

The aim of this study was to explore the relationship between disease severity and the HRQoL of people with dementia and their family carers using several disease-specific and generic measures, using cross-sectional baseline data from a cohort study (MODEM program). The study collected, among others, DEMQOL, EQ-5D-3L, CASP-19 and SF-12. The EQ-5D is reported in the following paragraphs, as the one most aligned with the instrument collected in Clarity AD used in the economic evaluation. As the repose rate of the study was not reported, the non-response bias was not able to be evaluated. Despite AD represented most of the diagnosis (>60%), other dementia diagnoses were also included in the study. A priory expectation was that patients would experience a worsening in HRQoL with AD progression (74).

10.3.2 Data collection (Farina et al 2020)(74)

The analysis conducted by Farina et al. 2020 (74), were based on data collected in the MODEM cohort study (cross sectional). Missing values within standardised questionnaires

were handled in accordance with measure guidance, when available. Listwise deletion was adopted across analyses in the case of missing values. A series of multiple regression models were created, in which QoL outcomes were the dependent variables. In each model, factors were entered in a stepwise manner, first as single covariates and then multiple, to be able to identify the amount of explained variance in severity after accounting for the control variables (74).

10.3.3 HRQoL Results (Farina et al. 2020)(74)

307 participant dyads were consented into the study, 110 were classified as having mild dementia, 100 moderate, and 97 severe dementia. Mean (SD) self-reported EQ-5D-3L values were 0.8 (0.2) for Mild AD, 0.8 (0.2) for Moderate AD and not reported for severe AD. Mean (SD) proxy-reported EQ-5D-3L values were 0.7 (0.3) for Mild AD, 0.5 (0.3) for Moderate AD and 0.4 (0.3) for severe AD. The regressions indicated a significant association between residing in a care home and diminished EQ-5D-3L reported by proxy [unstandardised B coefficient -0.13 (95% C.I: -0.23, -0.03)] and no decrement in EQ-5D-3L self-reported [unstandardised B coefficient 0.00; (95% C.I: -0.12, 0.11)] (74).

10.3.4 HSUV and disutility results (Farina et al 2020)(74)

Table 44 summarises the main findings from Farina et al. 2020 (74).

Table 44 Overview of health state utility values (and disutilities) from Farina et al., 2020 (74)

	Results [SE]	Instrument	Tariff (value set) used	Comments
Mild AD	0.8 (02)	EQ-5D-3L self-reported	NR	Mean value
	0.7 (0.3)	EQ-5D-3L proxy-reported	NR	Mean value
Moderate AD	0.8 (02)	EQ-5D-3L self-reported	NR	Mean value
	0.5 (0.3)	EQ-5D-3L proxy-reported	NR	Mean value
Severe AD	0.4 (0.3)	EQ-5D-3L proxy-reported	NR	Mean value
Disutility	-0.13	EQ-5D-3L proxy-reported	NR	Disutility associated with residing in a residential care home

Abbreviation: AD =Alzheimer's disease; MCI =Mild Cognitive Impairment; NR = Not reported

10.3.5 Study design (Landeiro et al. 2020)(75)

This systematic literature review was conducted with the main aim to provide an overview of which instruments are used to assess HR-QoL in people with predementia AD, MCI, or dementia, and meta-analysed summarising their reported values at each stage of the disease and by type of respondent. Summary results were presented by respondent type, type of instrument, geographical location and, where possible, stage of disease. The prior expectation was that patients would experience a worsening in HRQoL with AD progression (75).

10.3.6 Data collection (Landeiro et al. 2020)(75)

A systematic literature review was conducted following the PRISMA guidelines. The protocol was registered with the PROSPERO international prospective register of systematic reviews (registration number CRD42017071416). A meta-analysis of EQ-5D data was conducted by pooling utility values across all studies by disease severity (MCI,

mild, mild to moderate, moderate and severe dementia; not specified) and by respondent (person with dementia, carer, public; not specified) using a fixed-effects approach) (75).

10.3.7 HRQoL Results (Landeiro et al. 2020)(75)

307 participant dyads were consented into the study, 110 were classified as having mild dementia, 100 moderate, and 97 severe dementia. Mean (SD) self-reported EQ-5D-3L values were 0.8 (0.2) for Mild AD, 0.8 (0.2) for Moderate AD and not reported for severe AD. Mean (SD) proxy-reported EQ-5D-3L values were 0.7 (0.3) for Mild AD, 0.5 (0.3) for Moderate AD and 0.4 (0.3) for severe AD. The regressions indicated a significant association between residing in a care home and diminished EQ-5D-3L reported by proxy [unstandardised B coefficient -0.13 (95% C.I: -0.23, -0.03)] and no decrement in EQ-5D-3L self-reported [unstandardised B coefficient 0.00; (95% C.I: -0.12, 0.11)] (75).

10.3.8 HSUV and disutility results (Landeiro et al. 2020)(75)

Pooled EQ-5D-derived utility values by disease severity showed no statistically significant difference between self-rated and proxy-rated values for patients with MCI (difference in weighted means −0.06, p =0.17). The difference between self-rated and proxy rated utilities increased with disease severity; people with severe dementia indicated having high utilities (weighted mean 0.82), whereas proxies suggested much lower utilities (weighted mean 0.36). These results demonstrated a statistically significant difference in utility values from mild dementia onward, with a difference of − 0.46 for people with severe dementia (P < 0.01) (75). The mean health state utility resulting from the meta-analysis are summarised in Table 45.

Table 45 Overview of health state utility values from Landeiro et al,. 2020 (75)

	Results [95% CI]	Instrument	Tariff (value set) used	Comments
MCI due to AD	0.86 (0.78, 0.93)	EQ-5D self-reported	NR	Weighted average
	0.80 (0.75, 0.85)	EQ-5D proxy-reported	NR	Weighted average
Mild AD	0.85 (0.80, 0.89)	EQ-5D self-reported	NR	Weighted average
	0.74 (0.69, 0.79)	EQ-5D proxy-reported	NR	Weighted average
Moderate AD	0.86 (0.76, 0.96)	EQ-5D self-reported	NR	Weighted average
	0.59 (0.47, 0.71)	EQ-5D proxy-reported	NR	Weighted average
Severe AD	0.82 (0.64,1.00)	EQ-5D self-reported	NR	Weighted average
	0.36 (0.18, 0.53)	EQ-5D proxy-reported	NR	Weighted average

Abbreviation: AD =Alzheimer's disease; MCI =Mild Cognitive Impairment; NR = Not reported

In Table 46 are summarised the utility values sourced from the literature and discussed in this submission. The values included in the model are described in Table 43.

Table 46 Overview of literature-based health state utility values (Farina et al., 2020 (74) & Landeiro et al., 2020 (75))

	Results [95% CI]	Instrument	Tariff (value set) used	Comments
MCI due to AD				
	0.86 (0.78, 0.93)	EQ-5D self-reported	NR	Weighted average

	Results [95% CI]	Instrument	Tariff (value set) used	Comments
Landeiro et al. 2020	0.80 (0.75, 0.85)	EQ-5D proxy-reported	NR	Weighted average
Mild AD				
Farina et al., 2020	0.8 (02)	EQ-5D-5L self-reported	NR	Mean value
	0.7 (0.3)	EQ-5D-5L proxy-reported	NR	Mean value
Landeiro et al., 2020	0.85 (0.80, 0.89)	EQ-5D self-reported	NR	Weighted average
	0.74 (0.69, 0.79)	EQ-5D proxy-reported	NR	Weighted average
Moderate AD				
Farina et al., 2020	0.8 (02)	EQ-5D-5L self-reported	NR	Mean value
	0.5 (0.3)	EQ-5D-5L proxy-reported	NR	Mean value
Landeiro et al., 2020	0.86 (0.76, 0.96)	EQ-5D self-reported	NR	Weighted average
	0.59 (0.47, 0.71)	EQ-5D proxy-reported	NR	Weighted average
Severe AD				
Farina et al., 2020	Severe AD	0.4 (0.3)	EQ-5D-5L proxy-reported	Not reported
Landeiro et al. 2020	0.82 (0.64,1.00)	EQ-5D self-reported	NR	Weighted average
	0.36 (0.18, 0.53)	EQ-5D proxy-reported		Weighted average
Disutility for institutionalisation				
Farina et al., 2020	-0.13	EQ-5D-5L proxy-reported	NR	Disutility associated with residing in a residential care home

Abbreviation: AD =Alzheimer's disease; MCI =Mild Cognitive Impairment; NR = not reported
Source: Farina et al 2020 (74), Landeiro et al. 2020 (75).

11. Resource use and associated costs

11.1 Medicine costs - intervention and comparator

Administration of lecanemab is based on the Clarity AD study, in which patients received biweekly infusions of lecanemab administered at a dose of 10 mg/kg. The lecanemab unit cost per package is DKK 2 280 for the 200 mg vial, and DKK 4 560 for the 500 mg vial.

As mentioned in section 3.4 and Appendix N, a maintenance dosing regimen of monthly infusions of lecanemab at a dose of 10 mg/kg after 18 months was approved by the FDA [redacted]

Table 47 Medicine costs used in the model

Medicine	Dose	Relative dose intensity	Frequency	Vial sharing
Lecanemab	200 mg	[redacted]	Every second week	No, tested in scenario analysis
Lecanemab	500 mg	[redacted]	Every second week	No, tested in scenario analysis

When vial sharing is not assumed (base case analysis), the lecanemab cost per dose is derived with consideration to minimising wastage, based on the distribution of patients' weight distribution from Clarity AD Core study (Table 48), and assuming the maximum dose for each weight interval. This results in an average cost per dose of 7 875 DKK (60). The base case analysis includes the cost of wastage (no vial sharing assumed).

If vial sharing is assumed (tested in a scenario analysis), the lecanemab cost per dose is based on the cost per mg, using the trial's patients' mean weight (69.93 kg,) derived from the ITT FAS+ ApoE ε4 non-carriers and heterozygotes (Europe, excluding Australia). This results in a cost per dose of 6 378 DKK.

Finally, the compliance rate of 95.26% derived from the Clarity AD Core study is applied (60). In the sensitivity analysis, the compliance rate derived from the 36-month OLE is tested (93.40%).

Time on treatment for lecanemab is estimated using the TTD from Clarity AD and extrapolated throughout the time horizon using a constant rate (section 8.1.2.1)

Table 48 Patients weight distribution and relative required numbers of vials

Weight interval	Frequency n (%) N=326	Numbers of vials (200mg)	Numbers of vials (500mg)
<40	[redacted]	0	1
40-50	[redacted]	0	1
50-60	[redacted]	1	1
60-70	[redacted]	1	1
70-80	[redacted]	0	2
80-90	[redacted]	0	2
90-100	[redacted]	0	2
100-110	[redacted]	1	2
110-120	[redacted]	1	2
120-130	[redacted]	0	3
130-140	[redacted]	0	3
140+	[redacted]	0	3

Source: Clarity AD (68)

11.2 Medicine costs – co-administration

Lecanemab is anticipated to be used alongside symptomatic treatments, which are also administered to patients in the SoC arm. Symptomatic treatments included in the analysis are memantine and AChEI (donepezil, rivastigmine, and galantamine). The proportion of

patients receiving symptomatic treatment in each health state is detailed in Table 49. As the usage of symptomatic treatment per health state is unknown in clinical practice, the distribution observed in Clarity AD was used and is the same across arms.

Table 49 Probability of receiving each symptomatic treatment, per health state

	MCI due to AD	Mild AD	Moderate AD	Severe AD	Source
Memantine	10%	21%	23%	15%	Clarity AD (68)
AChEIs	46%	57%	66%	82%	

Abbreviations: AD, Alzheimer's disease; AChEI, Acetylcholinesterase inhibitor; MCI, Mild cognitive impairment; SoC, Standard of care.

Costs related to symptomatic treatment are detailed in Table 50. The monthly costs are calculated by multiplying the treatment cost (Table 50) by the percentage of patients receiving the treatments in each health state, derived from Clarity AD (Table 49).

Table 50 Symptomatic treatments costs

	Dose (mg/day)	Pack size	Mg per unit	Pack cost (DKK)	% of patients	Cost per month (DKK)	Source
Memantine	20	100	10	37.00	-	22.52	Medicinpriser.dk
AChEI							
Donepezil	10	100	10	32.00	76.2%	19.45	Unit costs: Medicinpriser.dk Dosages: Fass.se (116)
Rivastigmine	4.5	112	4.5	85.50	16.1%		
Galantamine	16	84	16	300.00	7.71%		

Abbreviations: AChEI, Acetylcholinesterase inhibitor

11.3 Administration costs

The lecanemab administration cost is estimated using the cost per IV infusion. The cost of IV infusion (Table 51) was estimated using the Danish Health Data Authority's website Interactive DRG (117). Based on the unit cost and frequency of administration, the monthly costs associated with administration in the base case is DKK 4 374.30.

Table 51 Administration costs used in the model

Administration type	Frequency*	Unit cost [DKK]	DRG code	Reference
IV infusion	2.17 doses per month	2 012	DRG 01MA98, MDC01 1-dagsgruppe, pat. mindst 7 år	Unit cost: DRG 2025 (117) Frequency: Clarity AD (60)

Abbreviations: DKK, Danish kronor; IV, Intravenious.
Notes: *[redacted]

11.4 Disease management costs

Disease management costs by health state were sourced from Aye et al., 2024 (79), which is believed to be the most recent registry-based study estimating AD costs in the Nordics. In the article, a national registry-based cohort study from the Swedish registry for cognitive/dementia disorders (SweDem) is presented, investigating the direct medical and non-medical costs associated with AD across its severity spectrum, from MCI to Severe AD,

also examining a subset of amyloid-positive individuals, in community and institutional settings. The cost components included in the analysis were direct medical costs (outpatients and inpatients, while drug costs were not included to avoid double counting) and direct non-medical costs (including institutional care, home care, daytime activities, short term care and housing support) (Table 52).

Aye at al., 2024 (79) was considered the most detailed, complete and recent source for health state costs related to AD in the Nordics. In the model, direct costs include outpatient and inpatients costs, while institutionalisation, home care, daytime activities, short-term care and housing support were included as non-medical costs. Cost values have been implemented following the guidelines set out by the DMC.

Table 52 Disease management (direct medical and non-medical) costs used in the model (monthly)

Activity	Frequency	Direct medical cost [DKK]	Direct non-medical cost [DKK]	Reference
Community				
MCI due to AD	Every month (model cycle)	**19 184.52**	**9 721.17**	Aye at al 2024 (79)
Mild AD		**17 398.29**	**54 486.55**	
Moderate AD		**16 064.28**	**117 125.25**	
Severe AD		**19 419.94**	**270 941.87**	
Institution				
MCI due to AD	Every month (model cycle)	**0.00**	**0.00**	
Mild AD		**16 543.37**	**833 558.38**	
Moderate AD		**15 044.68**	**833 558.38**	
Severe AD		**17 864.46**	**833 558.38**	

Abbreviations: AD = Azherimer's disease; DKK, Danish kronor; MCI = mild congintive impairment.

11.5 Costs associated with management of adverse events

The adverse events included in the analysis and their frequency are described in section 9.1. All unit costs were applied as one-off costs at the beginning of the time horizon.

As per severity definition used in Clarity AD, AEs that required hospitalisation were serious AEs. In addition, it was assumed that 75% of patients experiencing severe symptomatic ARIA-E and severe symptomatic isolated ARIA-H would require hospitalisation, based on clinical expert opinion.

AEs and associated resources used are described in Table 53. In the absence of published Danish 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., 2023 (80) and international clinical experts.

Table 53 AE management

AE	Severity	Management
IRR	**Grade 1**	• None

	Grade 2	• Oral cetirizine hydrochloride 10mg, repeated once daily until symptoms fully resolve Paracetamol 500-1000 mg, repeated every 6 hours until symptoms fully resolve¥ • Expected to resolve <24 hours – but in practice likely to be approximately 2-4 hours only
	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 cetirizine hydrochloride 10mg 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 Asymptomatic ¥	**Mild**	• 1 outpatient neurology repeat consultation • 1 MRI scan
	Moderate	• 1 outpatient neurology repeat consultation • 1.5 MRI scans
	Severe	• 2 outpatient neurology repeat consultations • 2.5 MRI scans
ARIA-E symptomatic ¥	**Mild-Moderate**	• 1 outpatient neurology repeat consultation • 2 MRI scans
	Severe	• 1 outpatient neurology repeat consultation • 2 MRI scans • 0.8 hospitalisations
ARIA-H Asymptomatic ¥		• 1 outpatient neurology repeat consultation • 1 MRI scan
		• 1 outpatient neurology repeat consultation • 1.5 MRI scans
		• 1.5 outpatient neurology repeat consultations • 2 MRI scans
ARIA-H Symptomatic ¥		• 1 outpatient neurology repeat consultations • 1 MRI scan
		• 1.5 outpatient neurology repeat consultations • 1.5 MRI scans
		• 1.5 outpatient neurology repeat consultations • 2 MRI scans • 0.8 hospitalisations

Source: Cummings et al. 2023 (80); Clarity AD CSR (60).
Abbreviations: AE = adverse event; ARIA-E = amyloid related imaging abnormality-oedema/effusion; ARIA-H = amyloid related imaging abnormality-microhaemorrhages and haemosiderin deposits; IRR = Infusion related reactions
Notes: ¥ Clinical opinion.

All unit costs were applied as one-off costs at the beginning of the time horizon. The drug costs associated with the resources described above are presented in Table 54.

Table 54 Drug unit costs associated with management of adverse events (pharmaceutical)

Treatment	Mg per dose	Pack size	Mg/unit	Pack cost (DKK)
Oral methylprednisolone	160	50	32	239.46
Cetirizine hydrochloride	10	50	10	87.95
Paracetamol	500	320	500	37.60
Oral dexamethasone	0.75	100	1	518.18

Abbreviations: AD = Azherimer's disease; DKK, Danish kronor; MCI = mild congintive impairment.

Visit costs related to managing adverse events include clinical visits, hospitalisation, and MRI due to ARIA. Treatment costs related to managing adverse events are presented in Table 55.

Table 55 Cost associated with management of adverse events (health care resource)

	DRG code	Unit cost/DRG tariff (DKK)
ARIA hospitalisation	01MA98	2,021.00
MRI	30PR02	2,701.00
GP visit	NA*	821.94

Abbreviations: ARIA, Amyloid-related imaging abnormality; DKK, Danish kronor; GP, General practitioner; MRI, Magnetic resonance imaging.
Notes: * Cost associated with GP visit is based on Værdisætning af enhedsomkostninger.

11.6 Subsequent treatment costs

N/A

Table 56 Medicines of subsequent treatments

Medicine	Dose	Relative dose intensity	Frequency	Vial sharing
N/A	N/A	N/A	N/A	N/A

11.7 Patient costs

Transportation (DKK 140.00 per visit) and patients costs (DKK 188.00 per hour) are included in the economic analysis as indicated in the DMC guidelines with unit cost sourced from the DMC's catalogue of unit costs, The inputs regarding number of trips and time spent in relation to treatment are shown in Table 57.

In response to the DMC request on May 20, 2025, a scenario was included assuming that 30% of patients may require caregiver support for healthcare visits, in attempt to reflect real-world variability in patient needs.

Table 57 Patient costs used in the model

Activity	Time spent [hours]
IV administration	Assumed 1 hour for the infusion + 30 minutes observation afterwards and trips to and from the hospital (total 2 h)
Monitoring visits (MRI)	
Diagnostic test	
ARIA hospitalisation	Assumed up to 6 days and 12 awake patient hours per day
GP visit	Assumed 0.5 hour

Abbreviations: GP, General practitioner; IV, intravenous; MRI, Magnetic resonance imaging.

11.8 Other costs (e.g. costs for home care nurses, out-patient rehabilitation and palliative care cost)

N/A

11.8.1 Diagnostic costs

The cost of genetic testing to establish ApoE ε4 carrier status was included for all patients in the lecanemab arm in the analysis. This genetic test is not currently routinely used in clinical practice; therefore, the unit cost of the test was sourced from ThermoFisher

Scientific (DKK 1605) and added to the cost of an outpatient specialist consultation (DKK 821.94 derived from the unit cost catalogue v 1.8 2024 (118), inflated to 2025 prices using a CPI 117.7). It is worth noting that the genetic test unit cost is likely overestimated in this analysis, as it is derived from a private company. For comparison, the same cost was sourced from the national pricelist in Sweden and corresponded to approximately DKK 764.50 (SEK 1138) (119). Finally, it was assumed that 50% of patients tested will also undergo additional genetic counselling, this cost was assumed to be equal to the specialist consultation. In the analysis, the cost of genetic testing also accounted for the proportion of patients that are ApoE ε4 homozygous (15.3%) covering the entire amyloid beta confirmed population in the lecanemab arm.

At diagnosis, patients were assumed to undergo a biomarker test as CSF or a PET scan. The unit cost of each test was sourced using DRG 09PR04 *Biopsi og væskeudsugning, overfladisk* for CSF (DKK 5,493) and DG309/ WCBMPXYXX) (*Alzheimers sygdom* UNS/MR *Cerebrum ifm*. PET/MR - 36PR06 *Klinisk fysiologi/nuklearmedicin grp*) for PET scan (DKK 5,287) for the year 2025. The proportion of patients receiving each test were assumed to be 90% and 10% respectively, based on expert opinion [221].

11.8.2 Monitoring costs

Patients on lecanemab treatment undergo 5 MRIs during the first year of treatment, and 1 every year from year 2 and beyond, as recommended in the SmPC (1). The unit cost for an MRI was sourced using DRG (117) 30PR02 MR-*scanning, kompliceret* (DKK 2701) for the year 2025.

12. Results

In the economic model, structural calculations are implemented in order to account for a possible volume based managed entry agreement (MEA). The structure implemented includes 5 possible steps of discount based on the expected number of vials sold. As agreed with the DMC, the details (discount levels, expected number of vials sold in each step) of the MEA is currently not accounted for in the economic model and will be defined and implemented following submission. Therefore, in section 12 the MEA results are not currently reported.

12.1 Base case overview

An overview of the base case including the key aspects of the analysis is provided in Table 58.

Table 58 Base case overview

Feature	Description
Comparator	SoC
Type of model	Markov model
Time horizon	30 years (lifetime)
Treatment line	First line. Subsequent treatment lines not included.
Measurement and valuation of health effects	Health-related quality of life measured with EQ-5D-5L in Clarity AD for MCI due to AD and Mild AD (68). Danish population weights were used to estimate health-state utility values. Values for Moderate AD and Severe AD

	calculated based on Clarity AD data and differences between severity specific utility from the literature (75).
Costs included	Diagnosis, Medicine costs, Administration cost, Disease management costs, Costs of adverse events, Patient and relatives' costs (time and transportation)
Dosage of medicine	Based on weight
Average time on treatment	Lecanemab: [redacted] years (undiscounted) SoC: -
Inclusion of waste	Yes, wastage cost is included in the base case (no vial sharing assumed)

Average time in model health state (Life years undiscounted)	Lecanemab	SoC
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; MCI = Mild cognitive impairment; SoC = standard of care

12.1.1 Base case results

Table 59 presents the base case results. Treatment with lecanemab is associated with increased drug and administration costs while providing saving in disease management costs, (despite these including lecanemab diagnosis, monitoring, symptomatic treatments costs and health state related costs). Finally, lecanemab is associated with higher AE and patients' costs compared to SoC. When considering outcomes, patients treated with lecanemab spend less time in the Severe AD health state and accrue more QALYs in MCI due to AD and Mild AD.

Table 59 Base case results, discounted estimates

	Lecanemab	SoC	Difference
Medicine costs	[redacted]	[redacted]	[redacted]
Medicine costs – co-administration	[redacted]	[redacted]	[redacted]
Administration	[redacted]	[redacted]	[redacted]
Disease management costs	[redacted]	[redacted]	[redacted]
Costs associated with management of adverse events	[redacted]	[redacted]	[redacted]
Subsequent treatment costs	[redacted]	[redacted]	[redacted]
Patient costs	[redacted]	[redacted]	[redacted]
Palliative care costs	[redacted]	[redacted]	
Total costs	[redacted]	[redacted]	[redacted]
Life years gained (MCI due to AD)	[redacted]	[redacted]	[redacted]
Life years gained (Mild AD)	[redacted]	[redacted]	[redacted]

Life years gained (Moderate AD)	[redacted]	[redacted]	[redacted]
Life years gained (Severe AD)	[redacted]	[redacted]	[redacted]
Total life years	[redacted]	[redacted]	[redacted]
QALYs (MCI due to AD)	[redacted]	[redacted]	[redacted]
QALYs (Mild AD)	[redacted]	[redacted]	[redacted]
QALYs (Moderate AD)	[redacted]	[redacted]	[redacted]
QALYs (Severe AD)	[redacted]	[redacted]	[redacted]
QALYs (adverse reactions)	[redacted]	[redacted]	[redacted]
Total QALYs	[redacted]	[redacted]	[redacted]
Incremental costs per life year gained (DKK)		[redacted]	
Incremental cost per QALY gained (ICER, DKK)		[redacted]	

Abbreviations: AD = Alzheimer's disease; ICER = Incremental cost effectiveness ratio; MCI = mild cognitive impairment; QALY = Quality adjusted life years

12.2 Sensitivity analyses

12.2.1 Deterministic sensitivity analyses

The deterministic sensitivity analysis was conducted on 138 variables included in the economic model. Table 60 summarises the 10 with the highest impact on the ICER. These include the HR used to estimate treatment effect in the long-term, the Mild AD utility from Landeiro et al., 2020 (75), and the lecanemab discontinuation rate.

Table 60 One-way sensitivity analyses results

	Change	Reason / Rational / Source	Incremental cost (DKK)	Incremental benefit (QALYs)	ICER (DKK/QALY)
Base case			[redacted]	[redacted]	[redacted]
TTW HR, copy-increments control-based multiple imputation, CDR-SB - combined	[redacted]	Lower and upper CI	[redacted]	[redacted]	[redacted]
	[redacted]		[redacted]	[redacted]	[redacted]
Utility: Landeiro (carer as proxy) - Mild AD	[redacted]	Lower and upper CI	[redacted]	[redacted]	[redacted]
	[redacted]		[redacted]	[redacted]	[redacted]
Discontinuation rate: Clarity, all cause - lecanemab, core combined data	[redacted]	Lower and upper CI	[redacted]	[redacted]	[redacted]
	[redacted]		[redacted]	[redacted]	[redacted]
Lecanemab cost of administration	[redacted]	+/- 20%	[redacted]	[redacted]	[redacted]
	[redacted]		[redacted]	[redacted]	[redacted]
Mortality rate: Crowell - severe AD	[redacted]	Lower and upper CI	[redacted]	[redacted]	[redacted]
	[redacted]		[redacted]	[redacted]	[redacted]
Mortality rate: Crowell - MCI due to AD	[redacted]	Lower and upper CI	[redacted]	[redacted]	[redacted]
	[redacted]		[redacted]	[redacted]	[redacted]

Direct, non-medical care costs, patients, Aye et al., 2024 - Severe AD	[redacted]	+/-20%	[redacted]	[redacted]	[redacted]
Potashman, MCI due to AD to mild AD	[redacted]	+/-20%	[redacted]	[redacted]	[redacted]
Potashman, mild AD to moderate AD	[redacted]	+/-20%	[redacted]	[redacted]	[redacted]
Mean age – Clarity AD population	[redacted]	Lower and upper CI	[redacted]	[redacted]	[redacted]

Abbreviations: AD = Alzheimer's disease; HR = Hazard ratio; ICER = Incremental cost effectiveness ratio; MCI = mild cognitive impairment; QALY = Quality adjusted life years; TTW = time to worsening

Figure 27 Tornado diagram

Abbreviations: AD = Alzheimer's disease; HR = Hazard ratio; ICER = Incremental cost effectiveness ratio; QALY = Quality adjusted life years

12.2.2 Probabilistic sensitivity analyses

The variables included in the PSA are listed in the "Control" sheet in the model. From this sheet, the user can select what variable to include/exclude from the analysis and which distribution to select for each parameter from column G. For values not empirically estimated, an arbitrary uncertainty of +/- 20% was applied. The results of the PSA are presented in Table 61.

Table 61 Probabilistic results of economic analysis

Incr. cost per QALY gained, DKK	Probabilistic
ICER vs SoC	[redacted]

Abbreviations: ICER = Incremental cost effectiveness ratio; QALY = Quality adjusted life year; SoC = Standard of care

Figure 28 shows the cost effectiveness acceptability curve. Figure 29 presents the cost effectiveness plane including all the 1000 PSA iterations, which are all located in the north-west quadrant of the plane, indicating that lecanemab is more effective and more costly than SoC in 100% of the iterations. The convergence plot in Figure 30 indicates convergency at around 200 iterations.

Figure 28 Cost effectiveness acceptability curve

Abbreviations: QALY = Quality adjusted life year; SoC = Standard of care; WTP = Willingness to pay

Figure 29 Scatter plot derived from PSA

Abbreviations: QALY = Quality adjusted life year; PSA = Probabilistic sensitivity analysis; SoC = Standard of care

Figure 30 Convergence plot

Abbreviations: QALY = Quality adjusted life year; PSA = Probabilistic sensitivity analysis; SoC = Standard of care

12.2.3 Scenario analysis

Several scenarios were conducted to test the main assumption taken in the economic analysis. The scenarios resulting in the lowest ICER were: maintenance dosing

assuming a baseline age of 60 years old [redacted] and a [redacted] Other scenarios that decrease the ICER include using TTW HR from Clarity AD core study, separated by health state [redacted] excluding drug wastage from the acquisition cost calculations [redacted] as well as using the TTW HR from Clarity AD Core study combined across health states [redacted] Using the 36 months OLE data to estimate TTW, TTD and compliance in the economic model increases the results by 3%. However, using the 48 months data brings results down [redacted]

Of the additional scenarios included after the first DMC round of review (May 20, 2025), only using patients reported values from Landeiro et al., 2020 to derive Moderate and Severe AD utilities have a significant impact on the results [redacted] derived from the difference observed between self- and proxy- reported values. The study highlighted that these differences might stem from factors such as patients' adaptation to their condition, reduced insight into their health status, or biases introduced by proxies' own stress levels and perceptions. Consequently, careful consideration is recommended particularly in advanced stages of cognitive decline, to ensure accurate assessment and interpretation of the results.

Table 62 Scenario analysis result

Description	ICER (DKK)	Difference from base case (%)
Drug wastage excluded	[redacted]	[redacted]
All patients starting in MCI	[redacted]	[redacted]
Use core study separated HRs for time to worsening - CDR-SB	[redacted]	[redacted]
Use core study combined HRs for time to worsening - CDR-SB	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
Continue treatment in institution	[redacted]	[redacted]
Baseline age: 60	[redacted]	[redacted]
Natural history data from model start	[redacted]	[redacted]
Institutionalisation source: Belger	[redacted]	[redacted]
MCI due to AD, mortality HR = 1	[redacted]	[redacted]
Patient utility source moderate and severe AD: Farina	[redacted]	[redacted]
36 months Clarity AD OLE scenario (TTW, TTD and compliance)	[redacted]	[redacted]
No waning	[redacted]	[redacted]
Maintenance dosing	[redacted]	[redacted]
Inclusion disutilities of AE	[redacted]	[redacted]
Use of patient reported values from Landeiro et al., 2020	[redacted]	[redacted]
Use of Global CRD as model endpoint	[redacted]	[redacted]
Use of health state utilities (not treatment specific)	[redacted]	[redacted]
Inclusion of caregivers time and transportation costs	[redacted]	[redacted]

Description	ICER (DKK)	Difference from base case (%)
48 months Clarity AD OLE scenario (TTW, TTD and compliance)	[redacted]	[redacted]

Abbreviations: AD= Alzheimer's disease; AE = Adverse events; CDR-SB = Clinical dementia rate – sum of boxes; HR = Hazard ratio; MCI = Mild cognitive impairment; OLE = Open label extension; QALY = Quality adjusted life year; PSA = Probabilistic sensitivity analysis; TTD = Time to discontinuation; TTW = Time to worsening.

13. Budget impact analysis

NCumber of patients (including assumptions of market share)

The number of patients included in this application and the assumptions taken to calculate them are described in section 3.2, including the expected lecanemab uptake, which was considered 100%.

Table 63 Number of new patients expected to be treated over the next five-year period if the medicine is introduced (adjusted for market share)

	Year 1	Year 2	Year 3	Year 4	Year 5
			Recommendation		
Lecanemab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SoC	0	0	0	0	0
			Non-recommendation		
Lecanemab	0	0	0	0	0
SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: SoC = Standard of care

Budget impact

The budget impact estimates the results of the cost-analysis described in section 11 of this application, with no discounting applied and excluding patient costs.

Table 64 Expected budget impact of recommending the medicine for the indication

	Year 1 (DKK)	Year 2 (DKK)	Year 3 (DKK)	Year 4 (DKK)	Year 5 (DKK)
The medicine under consideration is recommended	[redacted]				
The medicine under consideration is NOT recommended	[redacted]				
Budget impact of the recommendation	[redacted]				

14. List of experts

[redacted]

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Appendix A. Main characteristics of studies included

Table 65 Main characteristic of studies included

Trial name: CLARITY AD Core Study	NCT number: 03887455
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.
Publications – title, author, journal, year	van Dyck CH, Swanson CJ, Aisen P, Bateman RJ, Chen C, Gee M, Kanekiyo M, Li D, Reyderman L, Cohen S, Froelich L, Katayama S, Sabbagh M, Vellas B, Watson D, Dhadda S, Irizarry M, Kramer LD, Iwatsubo T. Lecanemab in Early Alzheimer's Disease. N Engl J Med. 2023 Jan 5;388(1):9-21. doi: 10.1056/NEJMoa2212948. Epub 2022 Nov 29. PMID: 36449413. (70)
Study type and design	Randomised, double-blind, parallel-group, placebo-controlled, multicentre phase 3 study. Enrolled patients were randomly assigned 1:1 based on a computer-generated randomization scheme. No crossover was allowed. The investigators, patients, and sponsor were masked during treatment assignment.
Sample size (n)	1521 (randomised, ApoE ε4 non-carriers or heterozygotes)
Main inclusion criteria	<u>Patients with MCI due to AD – intermediate likelihood</u> • Meet the NIA-AA core clinical criteria for MCI due to AD - intermediate likelihood • Have a global CDR score of 0.5 and CDR Memory Box score of 0.5 or greater at screening and baseline • Report a history of subjective memory decline with gradual onset and slow progression over the last 1 year before screening; must be corroborated by an informant <u>Patients with mild AD dementia</u> • Meet the NIA-AA core clinical criteria for probable AD dementia • Have a global CDR score of 0.5 to 1.0 and a CDR Memory Box score of 0.5 or greater at screening and baseline <u>All patients</u> • Objective impairment in episodic memory as indicated by at least one SD below age-adjusted mean in the WMS-IV LMII • Positive biomarker for brain amyloid pathology as measured by amyloid PET or CSF t-tau/Aβ 1-42 testing • Male or female participants aged ≥50 and ≤90 years, at the time of informed consent • MMSE score ≥22 at Screening and Baseline and ≤30 at screening and baseline • BMI >17 and <35 at screening • If receiving an approved AD treatment such as AChE inhibitors or memantine or both for AD, must be on a stable dose for at least 12 weeks prior to baseline

Trial name: CLARITY AD Core Study	NCT number: 03887455
	• Treatment-naive participants for AD can be entered into the study Unless otherwise stated, participants must have been on stable doses of all other (that is, non-AD-related) permitted concomitant medications for at least 4 weeks prior to baseline
Main exclusion criteria	• Any neurological condition that may be contributing to cognitive impairment above and beyond that caused by the participant's AD • History of TIA, stroke, or seizures within 12 months of screening • Any psychiatric diagnosis or symptoms that could interfere with study procedures in the participant • GDS score ≥8 at Screening • Contraindications to MRI scanning • 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 • Any immunological disease which is not adequately controlled, or which requires treatment with immunoglobulins, systemic mAbs (or derivatives of mAbs), systemic immunosuppressants, or plasmapheresis during the study • Participants with a bleeding disorder that is not under adequate control • Any other clinically significant abnormalities in physical examination, vital signs, laboratory tests, or ECG which require further investigation or treatment, or which may interfere with study procedures or safety • Any other medical conditions which are not stably and adequately controlled, or which in the opinion of the investigator(s) could affect the participant'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 6 months before screening unless it can be documented that the participant was randomized to placebo • Participation in a clinical study involving any anti-amyloid therapies unless it can be documented that the participant only received placebo • Participants who have any known prior exposure to lecanemab Participants who were dosed in a clinical study involving any new chemical entities for AD within 6 months prior to screening unless it can be documented that the participant was in a placebo treatment arm
Intervention	Lecanemab: 10mg/kg IV biweekly, 757 patients (randomised, ApoE ε4 non-carriers or heterozygotes)
Comparator(s)	Placebo: IV biweekly, 764 patients (randomised, ApoE ε4 non-carriers or heterozygotes)
Follow-up time	18 months

Trial name: CLARITY AD Core Study		NCT number: 03887455
Is the study used in the health economic model?	Yes	
Primary, secondary and exploratory endpoints	The primary endpoint was CDR-SB. Secondary endpoints are ADAS-Cog14, ADCOMS and ADCS MCI-ADL. Exploratory endpoints are Global CDR, EQ-5D-5L, QOL-AD and ZBI.	
Method of analysis	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 (120), 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 (Food and Drug Administration [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 ApoE ε4 carriers. Safety Analysis Set (SAS) population: • 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. o Lecanemab: 757 patients o Placebo: 764 patients Intention-To-Treat Full Analysis Set (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. o Lecanemab: 723 patients o Placebo: 743 patients Pharmacodynamic (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) o Amyloid PET SUVr (florbetaben) ▪ Lecanemab: 263 patients ▪ Placebo: 270 patients	

Trial name: CLARITY AD Core Study		NCT number: 03887455
	○ Amyloid PET SUVr (florbetapir) ▪ Lecanemab: 35 patients ▪ Placebo: 34 patients ○ Tau PET ▪ Lecanemab: 118 patients ▪ Placebo: 110 patients ○ Plasma Aβ42/40 ▪ Lecanemab: 647 patients ▪ Placebo: 685 patients ○ Plasma p-tau181 ▪ Lecanemab: 628 patients ▪ Placebo: 635 patients ○ CSF Aβ42 ▪ Lecanemab: 117 patients ▪ Placebo: 115 patients ○ CSF p-tau181 ▪ Lecanemab: 117 patients ▪ Placebo: 117 patients	
Subgroup analyses	• Symptomatic AD medication at baseline (Yes/No) • Clinical subgroup (MCI due to AD/mild AD) • ApoE4 status (Non carrier/heterozygous, homozygous) • Region • Sex • Age • Ethnicity • Race	
Other relevant information	N/A	

Trial name: CLARITY AD OLE trial		NCT number: 03887455
Objective	To evaluate the long-term efficacy and safety of lecanemab in participants with early AD based on the change from baseline in the CDR-SB and incidence of adverse events at 48 months of treatment in the extension study.	
Publications – title, author, journal, year	Data on file	
Study type and design	Phase 3, global, open-label, single-arm extension study	
Sample size (n)	1187 (OLE Treated Set)	
Main inclusion criteria	<u>OLE:</u> • Participants who have completed the Core Study OR de novo participants eligible for inclusion in SC vial substudy • Must continue to have a study partner who is willing and able to provide follow-up information on the participant throughout the course of the Extension Phase	

Trial name: CLARITY AD OLE trial	NCT number: 03887455
	SC vial substudy: • Willing to enter or continue in the amyloid PET substudy • Participants who have completed the Core Study OR de novo participants meeting all of the following: • Amyloid PET scan within 4 weeks of starting lecanemab • Documented diagnosis of early AD, MCI due to AD, or mild AD • MMSE score ≥22 and ≤30 at screening • Positive biomarker for brain amyloid pathology as indicated by PET with imaging agent • Age ≥50 and ≤90 years at time of informed consent If receiving approved AD treatment, stable dose for ≥12 weeks before screening
Main exclusion criteria	• Participants who discontinued early from the Core Study • Participants who develop the following conditions from the time of screening for the Core Study to the start of the Extension Phase o Any neurological condition that may be contributing to cognitive impairment above and beyond that caused by the participant's AD o Any psychiatric diagnosis or symptoms that could interfere with study procedures in the participant o Contraindications to MRI scanning o Other significant pathological findings on brain MRI during the Core Study o Hypersensitivity to lecanemab or any of the excipients, or to any monoclonal antibody treatment o Any immunological disease which is not adequately controlled, or which requires treatment with immunoglobulins, systemic monoclonal antibodies (or derivatives of monoclonal antibodies), systemic immunosuppressants, or plasmapheresis during the study o Any other clinically significant abnormalities in physical examination, vital signs, laboratory tests, or ECG, which in the opinion of the investigator require further investigation or treatment or which may interfere with study procedures or safety o Malignant neoplasms (except for basal or squamous cell carcinoma in situ of the skin, or localized prostate cancer in male participants) that are not stably and adequately controlled or which, based on the opinion of the investigator, may interfere with the participant's safety or participation in the study o Any other medical conditions which are not stably and adequately controlled, or which in the opinion of the investigator(s) could affect the participant's safety or interfere with the study assessments Severe visual or hearing impairment that would prevent the participant from performing psychometric tests accurately
Intervention	Lecanemab: 10 mg/kg IV biweekly

Trial name: CLARITY AD OLE trial		NCT number: 03887455
Comparator(s)	N/A	
Follow-up time	Extension study: Up to 48 months	
Is the study used in the health economic model?	Yes	
Primary, secondary and exploratory endpoints	The primary endpoints were incidence of AEs and changes in vital signs, ECGs, laboratory safety tests, suicidality assessments, ADA and MRI safety parameters, and change from Core Study baseline in CDR-SB. The exploratory endpoints were ADAS-Cog14, ADCOMS, ADC MCI-ADL, and modified iADRS. 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 gray matter region of interest (ROI), meta-temporal ROI, frontal ROI, cingulate ROI, parietal ROI, occipital ROI, medial temporal ROI, and temporal ROI and TauIQ global tau load), blood and CSF biomarkers, vMRI biomarkers, EQ-5D-5L, QOL-AD, and Zarit Burden Interview	
Method of analysis	OLE Treated Set: • Subjects who received at least 1 dose of study drug during the OLE study. The OLE Treated Set was used for subject disposition, protocol deviations, demographic and other baseline characteristics, and prior and concomitant medications during the OLE study. The analysis period includes the OLE study. Safety Analysis Set: • Subjects who received lecanemab (LEC10-BW) in the Core Study and/or OLE study. This analysis set consists of all subjects who received LEC10-BW in the Core Study and all subjects who received placebo in the Core Study and received LEC10-BW in the OLE study. Subjects who were randomized to placebo but inadvertently received more than one dose of LEC10-BW during the Core Study, are included in the Safety Analysis Set. Subjects who were randomized to LEC10BW in the Core Study are also included in the Safety Analysis Set, unless they never received any assigned dose. The Safety Analysis Set is used for safety analyses. The analysis period for safety analyses includes Core Study and OLE study in which subjects received LEC10-BW IV dose, which will be described as “LEC10-BW-treated period”. Subjects who received placebo in Core Study and then entered OLE study, only OLE study (i.e., only data collected in the OLE study) are included. Baseline in the safety analyses is the last non-missing assessment prior to the start of the period. Specifically, baseline is the OLE baseline for subjects who received LEC10-BW from the OLE study and is the Core Study baseline for subjects who received LEC10-BW from the Core Study. The safety data is presented in one group which includes all subjects in the Safety Analysis Set. OLE PK Analysis Set: Subjects who received at least 1 dose of study drug during the OLE study with at least 1 quantifiable lecanemab serum (analysis set for	

Trial name: CLARITY AD OLE trial		NCT number: 03887455
	serum) and or CSF concentration (analysis set for CSF) with a documented dosing history during the OLE study.	
Subgroup analyses	• Symptomatic AD medication at baseline (Yes/No) • Clinical subgroup (MCI due to AD/mild AD) • ApoE4 status (Non carrier/heterozygous, homozygous) • Region • Sex • Age • Ethnicity • Race	
Other relevant information	N/A	

Appendix B. Efficacy results per study

Results per study

Table 66 Results per study: CLARITY AD Core Study

Results of CLARITY AD Core Study (NCT03887455)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
Change from baseline in CDR-SB at 18 months, ApoE ε4 non-carriers and heterozygotes	Lecanemab	723	1.151 (0.987, 1.315)	-0.579	-0.811, -0.347	<0.001	N/A	N/A	N/A	Based on modified intention-to-treat analysis population. Adjusted mean change from baseline, SE and p-value are derived using mixed model repeat measures with treatment group, visit, treatment group by visit interaction, clinical subgroup, use of Alzheimer's disease symptomatic medication at baseline, ApoE ε4 carrier status, region, baseline value by visit interaction as fixed effects, and baseline value as covariate.	
	Placebo	743	1.730 (1.560, 1.900)								
Change in Amyloid PET (Centiloids) through 18 Months from baseline, ApoE ε4 non-carriers and heterozygotes	Lecanemab	298	-55.541 (-58.753, -52.329)	-59.437	-63.291, -55.582	<0.00001	N/A	N/A	N/A	Same as above	
	Placebo	302	3.895 (0.679–7.111)								

Results of CLARITY AD Core Study (NCT03887455)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
Proportion of Patients converting to amyloid negativity, ApoE ε4 non-carriers and heterozygotes	Lecanemab	[redacted]		[redacted]	N/A	<0.00001	N/A	N/A	N/A		
	Placebo	[redacted]									
Change from baseline in ADAS-Cog14 at 18 months, ApoE ε4 non-carriers and heterozygotes	Lecanemab	719	4.211 (3.517, 4.905)	-1.633	-2.555, -0.712	<0.001	N/A	N/A	N/A		
	Placebo	740	5.845 (5.161, 6.529)								
Change from baseline in ADCS MCI-ADL at 18 months, ApoE ε4 non-	Lecanemab	656	-3.469 (-4.153, -2.785)	2.234	1.342, 3.126	<0.00001	N/A	N/A	N/A		
	Placebo	675	-5.703 (-6.377, -5.029)								

Results of CLARITY AD Core Study (NCT03887455)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
carriers and heterozygotes											
Time to worsening of CDR-SB at 18 months, ApoE ε4 non-carriers and heterozygotes	Lecanemab	723	N/A	N/A	N/A	N/A	HR: 0.698	0.568, 0.858	0.00062		
	Placebo	743	N/A								
Change in HRQoL (patient-reported), ApoE ε4 non-carriers and heterozygotes	Lecanemab	700	[redacted]	[redacted]			N/A	N/A	N/A		
	Placebo	719	[redacted]								
Change in HRQoL	Lecanemab	698	[redacted]	[redacted]			N/A	N/A	N/A		

Results of CLARITY AD Core Study (NCT03887455)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
(partner as proxy), ApoE ε4 non-carriers and heterozygotes	Placebo	718	[redacted]								
Change in HRQoL (partner result), ApoE ε4 non-carriers and heterozygotes	Lecanemab	698	[redacted]	[redacted]	[redacted]		N/A	N/A	N/A		
	Placebo	718	[redacted]								

Table 67 Results per study: CLARITY AD OLE Study

Results of CLARITY AD OLE Study (NCT03887455)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
Change from baseline in CDR-SB at 36 months, ApoE ε4 non-carriers and heterozygotes	Lecanemab	743	[redacted]	[redacted]	N/A	N/A	N/A	N/A	N/A	A modelled placebo group based on an observational cohort (Alzheimer's Disease Neuroimaging Initiative [ADNI]) for CDR-SB is used to provide context since there is no placebo control group between 18 and 48 months. An a-priori matched observational cohort from ADNI (matched on baseline demographics and clinical characteristics) was created during the design of Clarity AD to aid in decision-making for the protocol design (for estimations of placebo decline to aid in power calculations, among others).	
	Modelled Placebo group from ADNI	346	[redacted]								
Change from baseline in CDR-SB at 48 months, ApoE ε4 non-carriers and heterozygotes	Lecanemab	743	4.400	-1.31	N/A	N/A	N/A	N/A	N/A		
	Modelled Placebo group from ADNI	346	5.708								
Change from baseline in	Lecanemab	[redacted]		[redacted]	[redacted]	N/A	N/A	N/A	N/A	Compare the patients on lecanemab with the patients	

Results of CLARITY AD OLE Study (NCT03887455)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
ADAS-Cog14 at 36 months, ApoE ε4 non-carriers and heterozygotes	Delayed start group	[redacted]								who switched to lecanemab when the 18 months were over	
Change from baseline in ADCS MCI-ADL at 36 months, ApoE ε4 non-carriers and heterozygotes	Lecanemab	[redacted]		[redacted]	[redacted]	N/A	N/A	N/A	N/A		
	Delayed start group	[redacted]									
TTW of CDR-SB at 36 months, ApoE ε4 non-carriers and heterozygotes	Lecanemab	[redacted]	N/A	N/A	N/A	N/A	[redacted]	[redacted]	N/A	Same as “Change from baseline in CDR-SB at 36 months”	
	Modelled Placebo group from ADNI	[redacted]	N/A								
TTW of CDR-SB at 48 months,	Lecanemab	723	N/A	N/A	N/A	N/A	HR: 0.70	0.58, 0.85	N/A	Same as “Change from baseline in CDR-SB at 36 months”	

Results of CLARITY AD OLE Study (NCT03887455)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
ApoE ε4 non-carriers and heterozygotes	Modelled Placebo group from ADNI	347	N/A								
Change in EQ-5D-5L (patient-reported) at 36 months, ApoE ε4 non-carriers and heterozygotes	Delayed start group	[redacted]									

Appendix C. Comparative analysis of efficacy

N/A

Appendix D. Extrapolation

N/A

D.1 Extrapolation of [effect measure 1]

D.1.1 Data input

D.1.2 Model

D.1.3 Proportional hazards

D.1.4 Evaluation of statistical fit (AIC and BIC)

D.1.5 Evaluation of visual fit

D.1.6 Evaluation of hazard functions

D.1.7 Validation and discussion of extrapolated curves

D.1.8 Adjustment of background mortality

D.1.9 Adjustment for treatment switching/cross-over

D.1.10 Waning effect

D.1.11 Cure-point

D.2 Extrapolation of [effect measure 2]

Appendix E. Serious adverse events

E.1 Core Study

E.1.1 Adverse event 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 (68).

A summary of TEAEs that occurred in Clarity AD is presented in Table 68. 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). AEs of special interest are presented in Medical Dictionary for Regulatory Activities (MedDRA) Preferred Terms throughout the document.

The overall incidence of TEAEs at 18 months in ApoE ε4 non-carriers and heterozygous patients was similar between placebo (81.2% [620/764]) and lecanemab (88.1% [667/757]) groups (Table 68) (83). TEAEs was higher in the lecanemab group (41.5% [314/757]) than in the placebo group (19.2% [147/764]) due to the higher incidence of ARIA and IRR in the lecanemab group (83). When events of infusion-related reactions, ARIA-E, and ARIA-H were excluded, incidence of TEAEs was similar between placebo [redacted] and lecanemab [redacted] groups (121).

Table 68 Overview of TEAEs at 18 Months – Clarity AD Core Study (Safety Analysis Set), ApoE ε4 Non-carriers and Heterozygotes

Category, n (%)	Lecanemab (N=757)	Placebo (N=764)
TEAEs	[redacted]	[redacted]
Treatment-related TEAEs[a]	[redacted]	[redacted]
Severe TEAEs	[redacted]	[redacted]
Serious TEAEs	[redacted]	[redacted]
Deaths	[redacted]	[redacted]
Other SAEs	[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: Eisai DOF (Table 14.3.1.2.1) (83)
Abbreviations: AE: Adverse event; ApoE ε4: Apolipoprotein E4; ARIA-E: Amyloid related imaging abnormalities with oedema or effusion; ARIA-H: Amyloid related imaging abnormalities with hemosiderin deposition; MedDRA: Medical dictionary for regulatory activities; SAE: Serious adverse event; TEAE: Treatment-emergent adverse event.
A 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. TEAEs of special interest include ARIA-E, ARIA-H (cerebral microhaemorrhages, superficial siderosis, macrohaemorrhage), infusion-related reactions, skin rash, other hypersensitivity, suicidal ideation and suicidal behaviour. For each row category, a subject with two or more adverse events in that category is counted only once.
MedDRA Version 25.0.

The most common treatment emergent adverse events overall were infusion-related reaction, fall, headache, ARIA with microhaemorrhages and hemosiderin deposits, and ARIA-E (Table 69) (83). Overall, the majority of TEAEs were mild and moderate in severity (83). Severe TEAEs were reported for [redacted] of placebo-treated patients and [redacted] of lecanemab-treated patients. The incidence of treatment-emergent serious AEs (TESAEs) was similar between the placebo [redacted] and lecanemab [redacted] groups (83). The incidence of treatment-related TESAEs were lower in the placebo group [redacted] than in the lecanemab group [redacted] (83). During the study period, deaths occurred in [redacted] patients in the lecanemab group, and [redacted] of patients in the placebo group (83, 122). No deaths were considered by the investigators to be related to lecanemab or occurred due to treatment-emergent ARIA with oedema or effusions (ARIA-E).

There was a lower incidence of TEAEs leading to study drug dose adjustment (including withdrawal, dose interruption, or infusion interruption) in the placebo group [redacted] than in the lecanemab group [redacted] (83). This is expected due to the management of IRR and ARIA-E, which were less common in the placebo group (Table 69). When infusion-related reactions, ARIA-E, and ARIA-H were excluded, the incidence of TEAEs leading to study drug dose adjustment was similar between placebo [redacted] and lecanemab [redacted] groups. TEAEs leading to discontinuation of the study drug occurred in [redacted] of the lecanemab group and in [redacted] of the placebo group (121).

Table 69 TEAEs with Incidence in ≥5% of Subjects in Any Treatment Group at 18 Months; Clarity AD Core Study (Safety Analysis Set), ApoE ε4 Non-carriers and Heterozygotes

MedDRA Preferred Term, n (%)	Lecanemab (N=757)	Placebo (N=764)
Any TEAE	[redacted]	[redacted]
Infusion-related reaction	[redacted]	[redacted]
Fall	[redacted]	[redacted]
Headache	[redacted]	[redacted]
ARIA with microhaemorrhages and haemosiderin deposits	[redacted]	[redacted]
ARIA-E	[redacted]	[redacted]

Urinary tract infection	[redacted]	[redacted]
COVID-19	[redacted]	[redacted]
Back pain	[redacted]	[redacted]
Arthralgia	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]
Dizziness	[redacted]	[redacted]

Source: Eisai DOF (Table 14.3.1.3.2) (83)

Abbreviations: AE = Adverse event; ApoE ε4 = Apolipoprotein E4; ARIA = Amyloid-related imaging abnormalities; ARIA-E = Amyloid related imaging abnormalities with oedema or effusion; COVID-19 = Coronavirus−19; MedDRA = Medical Dictionary for Regulatory Activities.

A 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. Subject with two or more adverse events with the same preferred term is counted only once for that preferred term. Cerebral microhaemorrhages include those deemed not ARIA-H by investigator. TEAEs are ordered by decreasing frequency in 10 mg/kg Biweekly group, then placebo group. For each row category, a subject with two or more adverse events in that category is counted only once. MedDRA Version 25.0.

E.1.2 Adverse events of special interest

Adverse events of special interest (AESIs) were infusion-related reactions, skin rash related to study drug, other hypersensitivity reactions related to study drug, ARIA-E, ARIA-H (defined as ARIA with superficial siderosis or cerebral microhaemorrhage), macrohaemorrhage (intracerebral haemorrhage), suicidal behaviour, and suicidal ideation (Table 70) (83). TEAEs of special interest occurred at a lower incidence in ApoE ε4 non-carriers and heterozygous carrier patients in the placebo group [redacted] than in the lecanemab group [redacted] at 18 months. Similarly, IRR and ARIA occurred at lower rates in the placebo group than in the lecanemab group (83).

Table 70 TEAEs of Special Interest at 18 Months; Clarity AD Core Study (Safety Analysis Set), ApoE ε4 Non-carriers and Heterozygotes

Preferred term	Number of patients, n (%)	
	Lecanemab (N=757)	Placebo (N=764)
Subjects with any TEAE of special interest	[redacted]	[redacted]
ARIA-E	[redacted]	[redacted]
ARIA-H	[redacted]	[redacted]
Superficial siderosis	[redacted]	[redacted]
Cerebral microhaemorrhage	[redacted]	[redacted]
Macrohaemorrhage	[redacted]	[redacted]
Infusion-related reactions	[redacted]	[redacted]
Skin rash	[redacted]	[redacted]
Other hypersensitivity	[redacted]	[redacted]
Suicidal behaviour	[redacted]	[redacted]
Suicidal ideation	[redacted]	[redacted]

Source: Eisai DOF (Table 14.3.2.6.1) (83)

Abbreviations: ApoE ε4 = Apolipoprotein E4; ARIA-E = Amyloid-related imaging abnormalities–oedema/effusion; ARIA-H = Amyloid-related imaging abnormalities–haemorrhage; TEAE = Treatment-emergent adverse event

A 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. IRR are defined if preferred term is infusion-related reaction or infusion site reaction.
Subject with two or more events is counted only once for that event.
MedDRA Version 25.0

E.1.2.1 ARIA

Overall, ARIA—including both asymptomatic and symptomatic—was observed in [redacted] in the lecanemab group, compared with [redacted] of patients in the placebo group of ApoE ε4 non-carriers and heterozygous patients in Clarity AD Core Study (83).

ARIA are common findings in brain magnetic resonance images from patients with AD. Increased occurrence of ARIA is associated with therapies that remove Aβ species like aducanumab, donanemab, and lecanemab (123, 124).

ARIA can present as brain oedema or sulcal effusion (ARIA-E) or as haemosiderin deposits resulting from microhaemorrhages (< 1cm) within the brain tissue or superficial siderosis on the pial surface (ARIA-H) (125). ARIA are transient and asymptomatic in most cases, typically occurring in early stages of treatment with monoclonal antibodies that remove Aβ species. 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 (124, 126). No systematic data exist on potential treatments for ARIA (126).

The exact mechanism for the occurrence of ARIA-E has not been elucidated, but probable explanations involve direct binding of Aβ antibodies to CAA or accelerated formation of CAA (55, 109, 127, 128). CAA is a pathology consisting of fibrillar Aβ, mainly Aβ1-40, deposited in the blood vessel walls and is a common occurrence in AD (app. 80% of AD patients) (129-131). Biochemical extraction of CAA fibrils from meningeal tissue demonstrate that Aβ1-40 is the major Aβ species in CAA fibrils (56).

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 (132). Throughout this document, ARIA refers to both overall ARIA-E, isolated ARIA-H and concurrent ARIA-H with ARIA-E.

Major risk factors for ARIA include anti-Aβ antibody exposure/dose, ApoE ε4 status, and the presence of preexisting microhaemorrhages as established by baseline MRI (124). Concomitant use of anticoagulation therapy may also elevate the risk of macrohaemorrhages (68). Other risk factors include the degree of brain Aβ deposition and the presence of pre-existing medical conditions that facilitate inflammatory responses such as autoimmune disorders (68).

E.1.2.1.1 Management of ARIA in the Clarity AD trial

In the Clarity AD Core Study, any subject who developed a single macrohaemorrhage, multiple (>10) microhaemorrhages cumulatively, symptomatic cerebral microhaemorrhages, or symptomatic superficial siderosis had treatment administration temporarily stopped, and had 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 are resolved radiographically and symptoms (if any) resolved.

E.1.2.1.2 ARIA-E

ARIA-E was observed in [redacted] of ApoE ε4 non-carriers and heterozygous carrier patients treated with lecanemab compared with [redacted] of patients on placebo at 18 months (Table 71) (83). Of those patients with ARIA-E, most treatment-emergent ARIA-E were radiographically mild (lecanemab: [redacted] placebo: [redacted] or moderate (lecanemab: [redacted] placebo: [redacted] in severity (83). [redacted] patients on placebo and [redacted] patients on lecanemab were categorized as having radiographically severe ARIA-E (83). Of these ARIA-E AEs, there were [redacted] treatment-related TESAEs due to ARIA-E in the placebo group and [redacted] treatment-related TESAEs due to ARIA-E in the lecanemab group (83). The incidence of symptomatic ARIA-E was low, observed in [redacted] patients on lecanemab and in [redacted] patients on placebo (83). Importantly, most ARIA-E radiographic events occurred early in treatment (within the first [redacted] doses), although ARIA-E can occur at any time and patients can have more than 1 episode. Resolution on magnetic resonance imaging (MRI) occurred in [redacted] of patients within 90 days, [redacted] within 120 days, and [redacted] by the end of Core Study, compared with [redacted] of patients on placebo (133).

In both lecanemab and placebo groups, the incidence of ARIA-E was higher in ApoE ε4 heterozygous carriers (lecanemab: [redacted] placebo: [redacted] than ApoE ε4 non-carriers (lecanemab: [redacted] placebo: [redacted] at 18 months (83).

Table 71 Treatment-Emergent ARIA-E at 18 Months -- Clarity AD Core Study (Safety Analysis Set), ApoE ε4 Non-carriers and Heterozygotes

	Lecanemab (N=757)	Placebo (N=764)
ARIA-E	[redacted]	[redacted]
ARIA-E by maximum radiographic severity		
Mild	[redacted]	[redacted]
Moderate	[redacted]	[redacted]
Severe	[redacted]	[redacted]
Missing	[redacted]	[redacted]
ARIA-E by ApoE ε4 genotype, n/N (%)		
ApoE ε4 non-carriers	[redacted]	[redacted]
ApoE ε4 heterozygous carriers	[redacted]	[redacted]

Source: Eisai DOF (Table 14.3.2.6.10.2, Table 14.3.2.6.10) (83)
A subject with two or more events is counted only once for that event.
ApoE ε4 carrier and non-carrier status and genotype are based on actual lab data.
Abbreviations: ApoE ε4 = apolipoprotein E4; ARIA = amyloid-related imaging abnormalities; ARIA-E = amyloid-related imaging abnormalities–oedema

E.1.2.1.3 ARIA-H

ARIA-H (including both concurrent with ARIA-E and isolated ARIA-H) was observed in [redacted] of ApoE ε4 non-carriers and heterozygous carrier patients treated with lecanemab compared with [redacted] of patients on placebo at 18 months (Table 72) (83). The majority of treatment-emergent ARIA-H was asymptomatic, with symptomatic ARIA-H reported in [redacted] of patients on lecanemab and [redacted] on placebo (134-136). In the lecanemab and placebo groups, the incidence of ARIA-H was higher in ApoE ε4 heterozygous carriers (lecanemab: [redacted] placebo: [redacted] than ApoE ε4 non-carriers (lecanemab: [redacted] placebo: [redacted] (Table 72) (83). The maximum radiographic severity of ARIA-H microhaemorrhage in patients on lecanemab was mild in [redacted] moderate in [redacted] and severe in [redacted] of patients; ARIA-H superficial siderosis was mild in [redacted] moderate in [redacted] and severe in [redacted] of patients (83). ARIA-H stabilized in [redacted] of patients on lecanemab compared with [redacted] of patients on placebo, either at the first follow-up MRI or within 20 weeks for most patients (83).

Additionally, a higher percentage of participants experienced concurrent ARIA-E and ARIA-H in the lecanemab group [redacted] compared with the placebo group [redacted] (83). A similar proportion of participants experienced isolated ARIA-H (ARIA-H not occurring concurrently with ARIA-E) in the lecanemab [redacted] and placebo [redacted] group (83). Most isolated ARIA-H was asymptomatic, with the incidence of symptomatic ARIA-H low at [redacted] in the lecanemab group (83). Symptoms were mostly mild to moderate in severity, with most common symptoms were headache, confusional state, and dizziness.

The overall incidence of macrohaemorrhage was generally low, with the incidence lower in the placebo group [redacted] than in the lecanemab group [redacted] (83). The majority of treatment-emergent macrohaemorrhage was asymptomatic, with symptomatic macrohaemorrhage reported in [redacted] of patients on lecanemab and [redacted] patients on placebo (83). Macrohaemorrhage occurs spontaneously in AD in the absence of anti-amyloid therapies due to underlying amyloid infiltration and resulting friability of cerebral blood vessels (CAA). Onset of macrohaemorrhage was distributed throughout the treatment period for both PBO and lecanemab groups. One death occurred in a patient on placebo who experienced macrohaemorrhage (137).

Table 72 Treatment-Emergent ARIA-H at 18 Months – Clarity AD Core Study (Safety Analysis Set), ApoE ε4 Non-carriers and Heterozygotes

	Lecanemab (N=757)	Placebo (N=764)
ARIA-H	[redacted]	[redacted]
Microhaemorrhage	[redacted]	[redacted]
Superficial siderosis	[redacted]	[redacted]
Macrohaemorrhage	[redacted]	[redacted]
ARIA-H by maximum radiographic severity, n/N (%)		

Mild	[redacted]	[redacted]
Moderate	[redacted]	[redacted]
Severe	[redacted]	[redacted]
Missing	[redacted]	[redacted]
ARIA-H by ApoE ε4 genotype, n/N (%)		
ApoE ε4 non-carriers	[redacted]	[redacted]
ApoE ε4 heterozygous carriers	[redacted]	[redacted]
Isolated ARIA-H (ARIA-H only, no ARIA-E)	[redacted]	[redacted]
Concurrent ARIA-E and ARIA-H	[redacted]	[redacted]

Source: Eisai DOF (Table 14.3.2.6.10.2, Table 14.3.2.6.10; Table 14.3.2.6.1) (83)

A subject with two or more events is counted only once for that event. a Symptomatic ARIA-H that was concurrent with ARIA-E was counted under symptomatic ARIA-E only. ApoE ε4 carrier and non-carrier status and genotype are based on actual lab data.

ApoE ε4: Apolipoprotein E4; ARIA: Amyloid-related imaging abnormalities; ARIA-H: Amyloid-related imaging abnormalities–haemorrhage; n: Number of subjects with an event in each category; N: number of subjects in treatment group; TEAE: Treatment-emergent adverse event.

E.1.2.2 Infusion-related reactions

Infusion-related reactions, which include the preferred terms 'infusion related reaction' and 'infusion site reaction', were reported for [redacted] of ApoE ε4 non-carriers and heterozygous carrier patients in the lecanemab group and [redacted] in the placebo group at 18 months (Table 73) (83). Most IRR were mild or moderate in severity, with Grade 1 (lecanemab: [redacted] placebo: [redacted] and Grade 2 reactions (lecanemab: [redacted] placebo: [redacted] being most common. [redacted] patients in the placebo arm reported Grade 3 or 4 reactions. In the lecanemab arm, [redacted] of patients [redacted] reported Grade 3 and [redacted] reported Grade 4 reactions, respectively (83). Of those who reported infusion-related reactions, most returned for the next study visit and some of those patients received preventative medications with subsequent infusions.

Table 73 Summary of IRRs by maximum grade at 18 Months – Clarity AD Core Study (Safety Analysis Set), ApoE ε4 Non-carriers and Heterozygotes

NCI-CTCAE Grade, n (%)	Lecanemab (N=757)	Placebo (N=764)
Any grade	[redacted]	[redacted]
Grade 1	[redacted]	[redacted]
Grade 2	[redacted]	[redacted]
Grade 3	[redacted]	[redacted]
Grade 4	[redacted]	[redacted]
Grade 5	[redacted]	[redacted]
Missing	[redacted]	[redacted]

Source: Eisai DOF (Table 14.3.2.6.4) (83)

Abbreviations: ApoE ε4 = Apolipoprotein E4; CTCAE = Common Terminology Criteria for Adverse Events; IRR = infusion-related reactions.

Study drug infusion reactions (within 24 hours of infusion) must be reported as AEs of interest. They will be graded according to the NCI-CTCAE, Version 4.0, grading of allergic/hypersensitivity reactions/cytokine release, as follows: Grade 1: mild reaction, infusion interruption not indicated, intervention not indicated; Grade 2: infusion interruption or treatment indicated, but responds promptly to symptomatic treatment (e.g., antihistamines, nonsteroidal anti-inflammatory drugs, IV fluids); prophylactic medications indicated for <24 hours; Grade 3: prolonged (e.g., not rapidly responsive to symptomatic medications or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization required for clinical sequelae

(e.g., renal impairment); Grade 4: life-threatening consequences; urgent treatment needed (e.g., vasopressor or ventilatory support); Grade 5: death

E.1.3 Suicidality and other safety parameters

No ApoE ε4 non-carriers and heterozygous patients in either treatment group committed suicide as of the Clarity AD Core Study safety analysis at 18 months (83). Only [redacted] of patients in the lecanemab group presented suicidal behaviour. Suicidal ideation was reported by [redacted] patients in the placebo group and [redacted] of patients in the lecanemab group (83).

E.2 OLE Study at 36 months

E.2.1 Adverse events overview

Overall, safety outcomes in the OLE phase are consistent with the Clarity AD Core Study. Of the [redacted] ApoE ε4 non-carriers and heterozygous carrier patients treated with lecanemab in the Clarity AD Core Study and/or the OLE phase at 36 months (Core + 18 months), [redacted] had at least 1 TEAE at 36 months (18 months of Core Study + 18 months of OLE), the majority of which were mild or moderate and non-serious. Severe TEAEs were reported for [redacted] patients (Table 74) (111).

Through 36 months, there were a total of [redacted] treatment-emergent deaths among those treated with lecanemab. Of these, [redacted] occurred during the OLE phase and [redacted] occurred during the Core Study phase (83, 111). [redacted] of the [redacted] occurring in the OLE phase were considered potentially treatment-related (83, 111).

TEAEs leading to study drug dose interruption and study drug withdrawal were reported for [redacted] and [redacted] patients, respectively (111). TEAEs of special interest (ARIA-E, ARIA-H, macrohaemorrhage, infusion-related reactions, skin rash, other hypersensitivity, suicidal ideation, and suicidal behaviour) were reported for [redacted] patients. Treatment-related TEAEs were reported for 44.5% (622/1366) patients (111).

Table 74 Overview of TEAEs at 36 months (18 Months of Core Study + 18 Months of OLE) – Clarity AD OLE LEC10-BW Treated Period (Safety Analysis Set), ApoE ε4 Non-carriers and Heterozygotes

Category, n (%)	Lecanemab (Core+OLE; N=1366)
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 hospitalization	[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: Eisai DOF (Table 14.3.1.2.1nh) (111)

Abbreviations: AE = Adverse event; ApoE ε4 = apolipoprotein E4; MedDRA = Medical dictionary for regulatory activities; OLE = Open-label extension; SAE = Serious adverse event; TEAE = Treatment-emergent adverse event. LEC10-BW-Treated Period includes Core Study and OLE Phase in which patients received lecanemab 10 mg/kg biweekly. Baseline is the last non-missing assessment prior to the start of the period. Specifically, baseline is the OLE baseline for patients who received lecanemab 10 mg/kg biweekly from the OLE phase, and is the Core Study baseline for patients who received lecanemab 10 mg/kg biweekly from the Core Study. A 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. For each row category, a patient with two or more AEs in that category is counted only once. Data collected after patients switch to/start subcutaneous dose are not included. MedDRA Version 25.0. 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 fatal row and is not counted in the nonfatal row.

E.2.2 Adverse events of special interest

Of the [redacted] ApoE ε4 non-carriers and heterozygous carrier patients in the LEC10-BW Treated Period, [redacted] of patients experienced a TEAE of special interest at 36 months (18 months of Core Study + 18 months of OLE) (Table 75) (138).

Table 75 TEAEs of Special Interest at 36 months (18 Months of Core Study + 18 Months of OLE) – Clarity AD OLE LEC10-BW Treated Period (Safety Analysis Set), ApoE ε4 Non-carriers and Heterozygotes

	Lecanemab (Core+OLE; N=1366), n (%)
Patients with any TEAE of special interest	[redacted]
ARIA-E	[redacted]
ARIA-H	[redacted]
Superficial siderosis	[redacted]
Cerebral microhaemorrhage	[redacted]
Macrohaemorrhage	[redacted]
Infusion-related reactions	[redacted]
Skin rash	[redacted]
Other hypersensitivity	[redacted]
Suicidal behaviour	[redacted]
Suicidal ideation	[redacted]

Source: Eisai DOF (Table 14.3.2.6.1anh) (138)

Abbreviations: AE = Adverse event; ApoE ε4 = apolipoprotein E4; ARIA-E = Amyloid-related imaging abnormality-oedema/effusion; ARIA-H = Amyloid-related imaging abnormality-haemorrhage; LEC10-BW = Lecanemab 10 mg/kg Biweekly; MedDRA = Medical dictionary for regulatory activities; OLE = Open-label extension; TEAE = Treatment-emergent adverse event.

LEC10-BW Treated Period includes Core Study and OLE Phase in which patients received lecanemab 10 mg/kg biweekly. Baseline is the last non-missing assessment prior to the start of the period. Specifically, baseline is the OLE baseline for patients who received lecanemab 10 mg/kg biweekly from the OLE phase and is the Core Study baseline for patients who received lecanemab 10 mg/kg biweekly from the Core Study. A 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. IRR are defined if preferred term is infusion related reaction or infusion site reaction. Patient with two or more events is counted only once for that event. Data collected after patients switch to/start subcutaneous dose are not included. MedDRA Version 25.0.

E.2.2.1 ARIA

E.2.2.1.1 ARIA-E

Of the [redacted] ApoE ε4 non-carriers and heterozygous patients in the LEC10-BW Treated Period, the overall incidence of ARIA-E was [redacted] at 36 months (18 months of Core Study + 18 months of OLE) (Table 76), with a slight increase in ARIA-E due to Core placebo-treated patients receiving lecanemab for the first time in the OLE phase (139, 140). The incidence of ARIA-E was lower in ApoE ε4 non-carriers [redacted] than in ApoE ε4 heterozygous carriers [redacted] (138).

Across both the Clarity AD Core Study and OLE Phase at 36 months (Core + 18 months), ARIA-E occurred early in treatment, with the majority (~90%) occurring in the first 6 months (141, 142). Most [redacted] ARIA-E resolved both radiographically and clinically by 4 months since onset (142). The majority of ARIA-E was mild to moderate radiographically in the OLE phase at 36 months (Table 76). Treatment-emergent serious ARIA-E occurred in [redacted] of patients (143).

Table 76 Treatment-Emergent ARIA-E at 36 Months (18 Months of Core Study + 18 Months of OLE) – Clarity AD OLE LEC10-BW Treated Period (Safety Analysis Set), ApoE ε4 Non-carriers and Heterozygotes

	Lecanemab (N=1366)
ARIA-E	[redacted]
ARIA-E by maximum radiographic severity, n/N (%)	
Mild	[redacted]
Moderate	[redacted]
Severe	[redacted]
Questionable	[redacted]
Missing	[redacted]
ARIA-E by ApoE ε4 genotype, n/N (%)	
ApoE ε4 non-carrier	[redacted]
ApoE ε4 heterozygous carriers	[redacted]

Source: Eisai DOF (Table 14.3.2.6.1anh(138); sCSR5 Table 14.3.2.6.10.2a)
Abbreviations: ApoE ε4 = Apolipoprotein E4; ARIA-E = Amyloid-related imaging abnormalities–oedema
LEC10-BW-Treated Period includes Core Study and OLE Phase in which subjects received lecanemab 10 mg/kg Biweekly. Baseline is the last non-missing assessment prior to the start of the period. Specifically, baseline is the OLE baseline for subjects who received placebo in the Core Study, and is the Core Study baseline for subjects who received lecanemab 10 mg/kg Biweekly in the Core Study. A 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. IRR are defined if preferred term is infusion related reaction or infusion site reaction. Subject with two or more events is counted only once for that event.
Data collected after subjects switch to/start subcutaneous dose are not included.

E.2.2.1.2 ARIA-H

The overall incidence rate of ARIA-H (including both concurrent and isolated ARIA-H) in ApoE ε4 non-carriers and heterozygous carriers patients was [redacted] at 36 months (18 months of Core Study + 18 months of OLE) (Table 77) (138). The incidence remained consistent with the Clarity AD Core Study, with a slight increase in ARIA-H due to Core placebo-treated patients receiving lecanemab for the first time during the OLE phase (144, 145). ARIA-H rates increase from ApoE ε4 non-carriers [redacted] to heterozygous ApoE ε4 carriers [redacted] (138). The majority of ARIA-H episodes was mild to moderate radiographically (Table 77). Only [redacted] of patients experiencing serious ARIA-H and [redacted] had symptomatic overall ARIA-H (144, 146).

Isolated ARIA-H occurred throughout the treatment period. Symptomatic isolated ARIA-H was reported by [redacted] of ApoE ε4 non-carriers and heterozygous carriers patients at 36 months (18 months of Core Study + 18 months of OLE) (147).

Table 77 Treatment-Emergent ARIA-H at 36 Months (18 Months of Core Study + 18 Months of OLE) – Clarity AD OLE LEC10-BW Treated Period (Safety Analysis Set), ApoE ε4 Non-carriers and Heterozygotes

	Lecanemab (N=1366)
ARIA-H	[redacted]
Microhaemorrhage	[redacted]
Superficial siderosis	[redacted]
Macrohaemorrhage	[redacted]
ARIA-H by maximum radiographic severity, n/N (%)	
Mild	[redacted]
Moderate	[redacted]
Severe	[redacted]
ARIA-H by ApoE ε4 genotype, n/N (%)	
ApoE ε4 non-carriers	[redacted]
ApoE ε4 heterozygous carriers	[redacted]
Isolated ARIA-H (ARIA-H only, no ARIA-E)	[redacted]
Concurrent ARIA-E and ARIA-H	[redacted]

Source: Eisai DOF (Table 14.3.2.6.1anh (138); Appendix 1 sCSR5 Table 14.3.2.6.10a (144); Appendix 1 Study 301 OLE sCSR5 Table 14.3.2.6.10.2a; Appendix 1 Study 301 OLE sCSR5 Table 14.3.2.6.10.6a).

Abbreviations: AE = Adverse event; ApoE ε4 = Apolipoprotein E4; ARIA-H = Amyloid-related imaging abnormality-haemorrhage; OLE = Open-label extension; TEAE = Treatment-emergent adverse event.

LEC10-BW Treated Period includes Core Study and OLE Phase in which patients received lecanemab 10 mg/kg biweekly. Baseline is the last non-missing assessment prior to the start of the period. Specifically, baseline is the OLE baseline for patients who received lecanemab 10 mg/kg biweekly from the OLE phase and is the Core Study baseline for patients who received lecanemab 10 mg/kg biweekly from the Core Study. A 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. A Patient with two or more events is counted only once for that event. ApoE ε4 carrier and non-carrier status and genotype are based on actual lab data. Data collected after patients switch to/start subcutaneous dose are not included.

E.2.2.2 Infusion-related reactions

Infusion-related reactions, which include the preferred terms 'infusion related reaction' and 'infusion site reaction', were reported for [redacted] of ApoE ε4 non-carriers and heterozygous carrier patients at 36 months (18 months of Core Study + 18 months of OLE) (Table 78) (83). Most IRR were mild or moderate in severity, with Grade 1 [redacted] and Grade 2 reactions [redacted] Of those who reported infusion-related reactions, most returned for the next study visit and some of those patients received preventative medications with subsequent infusions.

Table 78 Summary of IRRs by maximum grade at 36 Months (18 Months of Core Study + 18 Months of OLE) – Clarity AD OLE LEC10-BW Treated Period (Safety Analysis Set), ApoE ε4 Non-carriers and Heterozygotes

NCI-CTCAE Grade, n (%)	Lecanemab (N=1366)
Any grade	[redacted]
Grade 1	[redacted]
Grade 2	[redacted]
Grade 3	[redacted]
Grade 4	[redacted]
Grade 5	[redacted]
Missing	[redacted]

Source: Eisai DOF (Study 301 OLE sCSR5 Table 14.3.2.6.4a) (83)
Abbreviations: ApoE ε4 = Apolipoprotein E4; CTCAE = Common Terminology Criteria for Adverse Events; IRR = infusion-related reactions; OLE = Open-label.
Study drug infusion reactions (within 24 hours of infusion) must be reported as AEs of interest. They will be graded according to the NCI-CTCAE, Version 4.0, grading of allergic/hypersensitivity reactions/cytokine release, as follows: Grade 1: mild reaction, infusion interruption not indicated, intervention not indicated; Grade 2: infusion interruption or treatment indicated, but responds promptly to symptomatic treatment (e.g., antihistamines, nonsteroidal anti-inflammatory drugs, IV fluids); prophylactic medications indicated for <24 hours; Grade 3: prolonged (e.g., not rapidly responsive to symptomatic medications or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization required for clinical sequelae (e.g., renal impairment); Grade 4: life-threatening consequences; urgent treatment needed (e.g., vasopressor or ventilatory support); Grade 5: death

E.2.3 Suicidality and other safety parameters

At 36 months (18 months of Core Study + 18 months of OLE) in the Clarity AD study, [redacted] of patients reported suicidal behaviour and [redacted] reported suicidal ideation among ApoE ε4 non-carriers and heterozygous carrier patients compared to the Clarity AD Core Study (138, 148)

E.3 OLE study at 48 months

A summary of TEAEs and ARIA is presented in the Table 79 below.

Table 79 Summary of TEAE and ARIA (Exposure Adjusted)

	Lecanemab (Double-Blind + OLE) N = 1366		
	n	**%**	**Exposure Adjusted***
Adverse Event (AE)	1250	91.5%	35.9

Serious Adverse Event (SAE)	309	22.6%	8.9
Death[a]	29	2.1%	0.8
Deaths with concurrent ARIA or ICH irrespective of ARIA being cause of death	1	0.1%	<0.1
AEs Leading to Study Drug Withdrawal	126	9.2%	3.6
ARIA-E	151	11.1%	4.3
ARIA-H	292	21.4%	8.4
Isolated ARIA-H	187	13.7%	5.4
ICH[a]	8	0.6%	0.2

Source: Eisai DOF (99)
n, %, exposure-adjusted rate (per subject-year) are presented. OLE is based on IV datasets (as of 31 Mar 2025).
a: Includes all post-treatment events. Approx, approximate. yrs, years.
ARIA-E, amyloid related imaging abnormalities - edema; ARIA-H, ARIA with hemosiderin deposits; ICH, intracerebral hemorrhage.

Appendix F. Health-related quality of life

N/A

Appendix G. Probabilistic sensitivity analyses

Table 80 shows which data form the basis for the selected probability distributions used in the probabilistic analysis.

The distribution selected for each parameter was informed following the guideline in Briggs as suggested in the method's guide. The distribution selected was gamma for unit costs, beta for utilities, Dirichlet for probabilities, Normal for frequencies and for hazard ratios. The variables included, and the distribution assigned can be modified by the user in the economic model, in the Control sheet.

Table 80 Overview of parameters in the PSA

Input parameter	Point estimate	Lower bound	Upper bound	Probability distribution
Mean age (years) - Clarity trial population	[redacted]	[redacted]	[redacted]	[redacted]
% female - Clarity trial population	[redacted]	[redacted]	[redacted]	[redacted]
Mean weight (kg) - ITT FAS Europe	[redacted]	[redacted]	[redacted]	[redacted]
Proportion of patients MCI due to AD (CDR-SB)	[redacted]	[redacted]	[redacted]	[redacted]
Institutionalisation rate: Knapp - Mild AD	[redacted]	[redacted]	[redacted]	[redacted]
Institutionalisation rate: Knapp - Moderate AD	[redacted]	[redacted]	[redacted]	[redacted]
Institutionalisation rate: Knapp - Severe AD	[redacted]	[redacted]	[redacted]	[redacted]
Institutionalisation rate: Belger - Mild AD	[redacted]	[redacted]	[redacted]	[redacted]
Institutionalisation rate: Belger - Moderate AD	[redacted]	[redacted]	[redacted]	[redacted]
Institutionalisation rate: Belger - Severe AD	[redacted]	[redacted]	[redacted]	[redacted]
Mortality rate: Crowell - MCI due to AD	[redacted]	[redacted]	[redacted]	[redacted]
Mortality rate: Crowell - Mild AD	[redacted]	[redacted]	[redacted]	[redacted]
Mortality rate: Crowell - Moderate AD	[redacted]	[redacted]	[redacted]	[redacted]
Mortality rate: Crowell - severe AD	[redacted]	[redacted]	[redacted]	[redacted]
Discontinuation rate: Clarity, all cause - lecanemab, core combined data	[redacted]	[redacted]	[redacted]	[redacted]

IRR, Grade 1, lecanemab - % of patients	[redacted]	[redacted]	[redacted]	[redacted]
IRR, Grade 2, lecanemab - % of patients	[redacted]	[redacted]	[redacted]	[redacted]
IRR, Grade 3, lecanemab - % of patients	[redacted]	[redacted]	[redacted]	[redacted]
ARIA-E, mild, lecanemab - % of patients	[redacted]	[redacted]	[redacted]	[redacted]
ARIA-E, moderate, lecanemab - % of patients	[redacted]	[redacted]	[redacted]	[redacted]
ARIA-E, severe, lecanemab - % of patients	[redacted]	[redacted]	[redacted]	[redacted]
ARIA-E, mild, lecanemab - % of patients	[redacted]	[redacted]	[redacted]	[redacted]
ARIA-E, moderate, lecanemab - % of patients	[redacted]	[redacted]	[redacted]	[redacted]
ARIA-E, severe, lecanemab - % of patients	[redacted]	[redacted]	[redacted]	[redacted]
Isolated ARIA-H, mild, lecanemab - % of patients	[redacted]	[redacted]	[redacted]	[redacted]
Isolated ARIA-H, moderate, lecanemab - % of patients	[redacted]	[redacted]	[redacted]	[redacted]
Isolated ARIA-H, severe, lecanemab - % of patients	[redacted]	[redacted]	[redacted]	[redacted]
ARIA-E, mild, lecanemab - % of patients	[redacted]	[redacted]	[redacted]	[redacted]
ARIA-E, moderate, lecanemab - % of patients	[redacted]	[redacted]	[redacted]	[redacted]
ARIA-E, severe, lecanemab - % of patients	[redacted]	[redacted]	[redacted]	[redacted]
IRR, Grade 1, SoC - % of patients	[redacted]	[redacted]	[redacted]	[redacted]
IRR, Grade 2, SoC - % of patients	[redacted]	[redacted]	[redacted]	[redacted]
ARIA-E, mild, SoC - % of patients	[redacted]	[redacted]	[redacted]	[redacted]
Isolated ARIA-H, mild, SoC - % of patients	[redacted]	[redacted]	[redacted]	[redacted]
Utility: Clarity (patient) - MCI due to AD, Jensen et al., 2021 CDR-SB, lecanemab	[redacted]	[redacted]	[redacted]	[redacted]
Utility: Clarity (patient) - Mild AD, Jensen et al., 2021 CDR-SB, lecanemab	[redacted]	[redacted]	[redacted]	[redacted]

Utility: Clarity (patient) - Moderate AD, Jensen et al., 2021 CDR-SB, lecanemab	[redacted]	[redacted]	[redacted]	[redacted]
Utility: Clarity (patient) - MCI due to AD, Jensen et al., 2021 CDR-SB, SoC	[redacted]	[redacted]	[redacted]	[redacted]
Utility: Clarity (patient) - Mild AD, Jensen et al., 2021 CDR-SB, SoC	[redacted]	[redacted]	[redacted]	[redacted]
Utility: Clarity (patient) - Moderate AD, Jensen et al., 2021 CDR-SB, SoC	[redacted]	[redacted]	[redacted]	[redacted]
Utility: Clarity (carer as proxy) - MCI due to AD, Jensen et al., 2021 CDR-SB, lecanemab	[redacted]	[redacted]	[redacted]	[redacted]
Utility: Clarity (carer as proxy) - Mild AD, Jensen et al., 2021 CDR-SB, lecanemab	[redacted]	[redacted]	[redacted]	[redacted]
Utility: Clarity (carer as proxy) - Moderate AD, Jensen et al., 2021 CDR-SB, lecanemab	[redacted]	[redacted]	[redacted]	[redacted]
Utility: Clarity (carer as proxy) - MCI due to AD, Jensen et al., 2021 CDR-SB, SoC	[redacted]	[redacted]	[redacted]	[redacted]
Utility: Clarity (carer as proxy) - Mild AD, Jensen et al., 2021 CDR-SB, SoC	[redacted]	[redacted]	[redacted]	[redacted]
Utility: Clarity (carer as proxy) - Moderate AD, Jensen et al., 2021 CDR-SB, SoC	[redacted]	[redacted]	[redacted]	[redacted]
Utility: Landeiro (carer as proxy) - Moderate AD	[redacted]	[redacted]	[redacted]	[redacted]
Utility: Landeiro (carer as proxy) - Severe AD	[redacted]	[redacted]	[redacted]	[redacted]
Utility: Farina (carer as proxy) - institution, MCI due to AD	[redacted]	[redacted]	[redacted]	[redacted]
Lecanemab cost of administration	[redacted]	[redacted]	[redacted]	[redacted]
MRI cost	[redacted]	[redacted]	[redacted]	[redacted]
Year 1 MRI frequency	[redacted]	[redacted]	[redacted]	[redacted]
Year 2 MRI frequency	[redacted]	[redacted]	[redacted]	[redacted]
Year 3 MRI frequency	[redacted]	[redacted]	[redacted]	[redacted]
Year 4+ MRI frequency	[redacted]	[redacted]	[redacted]	[redacted]
Cost of biomarker test, CSF	[redacted]	[redacted]	[redacted]	[redacted]
Cost of PET scan	[redacted]	[redacted]	[redacted]	[redacted]
Biomarker test, CSF (%)	[redacted]	[redacted]	[redacted]	[redacted]

Biomarker test, PET (%)	[redacted]	[redacted]	[redacted]	[redacted]
Donepezil, proportion of patients	[redacted]	[redacted]	[redacted]	[redacted]
Rivastigmine, proportion of patients	[redacted]	[redacted]	[redacted]	[redacted]
Clarity-AD (CDR-SB), lecanemab, frequency of AChEI, MCI due to AD	[redacted]	[redacted]	[redacted]	[redacted]
Clarity-AD (CDR-SB), lecanemab, frequency of AChEI, mild AD	[redacted]	[redacted]	[redacted]	[redacted]
Clarity-AD (CDR-SB), lecanemab, frequency of AChEI, moderate AD	[redacted]	[redacted]	[redacted]	[redacted]
Clarity-AD (CDR-SB), lecanemab, frequency of AChEI, severe AD	[redacted]	[redacted]	[redacted]	[redacted]
Clarity-AD (CDR-SB), lecanemab, frequency of memantine, MCI d]ue to AD	[redacted]	[redacted]	[redacted]	[redacted]
Clarity-AD (CDR-SB), lecanemab, frequency of memantine, mild AD	[redacted]	[redacted]	[redacted]	[redacted]
Clarity-AD (CDR-SB), lecanemab, frequency of memantine, moderate AD	[redacted]	[redacted]	[redacted]	[redacted]
Clarity-AD (CDR-SB), lecanemab, frequency of memantine, severe AD	[redacted]	[redacted]	[redacted]	[redacted]
Clarity-AD (CDR-SB) SoC, frequency of AChEI, MCI due to AD	[redacted]	[redacted]	[redacted]	[redacted]
Clarity-AD (CDR-SB) SoC, frequency of AChEI, mild AD	[redacted]	[redacted]	[redacted]	[redacted]
Clarity-AD (CDR-SB) SoC, frequency of AChEI, moderate AD	[redacted]	[redacted]	[redacted]	[redacted]
Clarity-AD (CDR-SB) SoC, frequency of AChEI, severe AD	[redacted]	[redacted]	[redacted]	[redacted]
Clarity-AD (CDR-SB) SoC, frequency of memantine, MCI due to AD	[redacted]	[redacted]	[redacted]	[redacted]
Clarity-AD (CDR-SB) SoC, frequency of memantine, mild AD	[redacted]	[redacted]	[redacted]	[redacted]
Clarity-AD (CDR-SB) SoC, frequency of memantine, moderate AD	[redacted]	[redacted]	[redacted]	[redacted]
Clarity-AD (CDR-SB) SoC, frequency of memantine, severe AD	[redacted]	[redacted]	[redacted]	[redacted]
Direct medical costs, patient - Aye et al 2024 - MCI due to AD	[redacted]	[redacted]	[redacted]	[redacted]
Direct medical costs, patient - Aye et al 2024 - Mild AD	[redacted]	[redacted]	[redacted]	[redacted]

Direct medical costs, patient -Aye et al 2024- Moderate AD	[redacted]	[redacted]	[redacted]	[redacted]
Direct medical costs, patient - Aye et al 2024 - Severe AD	[redacted]	[redacted]	[redacted]	[redacted]
Direct medical costs, patient - Aye et al 2024 - Mild AD	[redacted]	[redacted]	[redacted]	[redacted]
Direct medical costs, patient - Aye et al 2024 - Moderate AD	[redacted]	[redacted]	[redacted]	[redacted]
Direct medical costs, patient - Aye et al 2024 - Severe AD	[redacted]	[redacted]	[redacted]	[redacted]
Direct, non-medical care costs, patients, Aye et al., 2024 - MCI due to AD	[redacted]	[redacted]	[redacted]	[redacted]
Direct, non-medical care costs, patients, Aye et al., 2024- Mild AD	[redacted]	[redacted]	[redacted]	[redacted]
Direct, non-medical care costs, patients, Aye et al., 2024- Moderate AD	[redacted]	[redacted]	[redacted]	[redacted]
Direct, non-medical care costs, patients, Aye et al., 2024 - Severe AD	[redacted]	[redacted]	[redacted]	[redacted]
Direct, non-medical care costs, patients, Aye et al., 2024 - Mild AD	[redacted]	[redacted]	[redacted]	[redacted]
Direct, non-medical care costs, patients, Aye et al., 2024n - Moderate AD	[redacted]	[redacted]	[redacted]	[redacted]
Direct, non-medical care costs, patients, Aye et al., 2024 - Severe AD	[redacted]	[redacted]	[redacted]	[redacted]
Potashman, MCI due to AD to AD	[redacted]	[redacted]	[redacted]	[redacted]
Potashman, MCI due to AD to mild AD	[redacted]	[redacted]	[redacted]	[redacted]
Potashman, MCI due to AD to moderate AD	[redacted]	[redacted]	[redacted]	[redacted]
Potashman, mild AD to MCI due to AD	[redacted]	[redacted]	[redacted]	[redacted]
Potashman, mild AD to moderate AD	[redacted]	[redacted]	[redacted]	[redacted]
Potashman, mild AD to severe AD	[redacted]	[redacted]	[redacted]	[redacted]
Potashman, moderate AD to mild AD	[redacted]	[redacted]	[redacted]	[redacted]
Potashman, moderate AD to severe AD	[redacted]	[redacted]	[redacted]	[redacted]
Potashman, severe AD to moderate AD	[redacted]	[redacted]	[redacted]	[redacted]
Lecanemab compliance, core study	[redacted]	[redacted]	[redacted]	[redacted]

Lecanemab compliance, OLE	[redacted]	[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]	[redacted]
Clarity-AD patient counts at 18 months (CDR-SB), lecanemab MCI due to AD to Mild AD	[redacted]	[redacted]	[redacted]	[redacted]
Clarity-AD patient counts at 18 months (CDR-SB), lecanemab MCI due to AD to Moderate AD	[redacted]	[redacted]	[redacted]	[redacted]
Clarity-AD patient counts at 18 months (CDR-SB), lecanemab MCI due to AD to Severe AD	[redacted]	[redacted]	[redacted]	[redacted]
Clarity-AD patient counts at 18 months (CDR-SB), lecanemab Mild AD to MCI due to AD	[redacted]	[redacted]	[redacted]	[redacted]
Clarity-AD patient counts at 18 months (CDR-SB), lecanemab Mild AD to Mild AD	[redacted]	[redacted]	[redacted]	[redacted]
Clarity-AD patient counts at 18 months (CDR-SB), lecanemab Mild AD to Moderate AD	[redacted]	[redacted]	[redacted]	[redacted]
Clarity-AD patient counts at 18 months (CDR-SB), lecanemab Mild AD to Severe AD	[redacted]	[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]	[redacted]
Clarity-AD patient counts at 18 months (CDR-SB), SoC MCI due to AD to Mild AD	[redacted]	[redacted]	[redacted]	[redacted]
Clarity-AD patient counts at 18 months (CDR-SB), SoC MCI due to AD to Moderate AD	[redacted]	[redacted]	[redacted]	[redacted]
Clarity-AD patient counts at 18 months (CDR-SB), SoC MCI due to AD to Severe AD	[redacted]	[redacted]	[redacted]	[redacted]
Clarity-AD patient counts at 18 months (CDR-SB), SoC Mild AD to MCI due to AD	[redacted]	[redacted]	[redacted]	[redacted]
Clarity-AD patient counts at 18 months (CDR-SB), SoC Mild AD to Mild AD	[redacted]	[redacted]	[redacted]	[redacted]

Clarity-AD patient counts at 18 months (CDR-SB), SoC Mild AD to Moderate AD	[redacted]	[redacted]	[redacted]	[redacted]
Clarity-AD patient counts at 18 months (CDR-SB), SoC Mild AD to Severe AD	[redacted]	[redacted]	[redacted]	[redacted]
GP visit	[redacted]	[redacted]	[redacted]	[redacted]
Hospitalisaiton cost, ARIA	[redacted]	[redacted]	[redacted]	[redacted]
Number of procedures/visits required, MRI, ARIA-E (asymptomatic), Mild	[redacted]	[redacted]	[redacted]	[redacted]
Number of procedures/visits required, MRI, ARIA-E (asymptomatic), Moderate	[redacted]	[redacted]	[redacted]	[redacted]
Number of procedures/visits required, MRI, ARIA-E (asymptomatic), Severe	[redacted]	[redacted]	[redacted]	[redacted]
Number of procedures/visits required, MRI, ARIA-E (symptomatic), Mild	[redacted]	[redacted]	[redacted]	[redacted]
Number of procedures/visits required, MRI, ARIA-E (symptomatic), Moderate	[redacted]	[redacted]	[redacted]	[redacted]
Number of procedures/visits required, MRI, ARIA-E (symptomatic), Severe	[redacted]	[redacted]	[redacted]	[redacted]
Number of procedures/visits required, MRI, Isolated ARIA-H (asymptomatic), Mild	[redacted]	[redacted]	[redacted]	[redacted]
Number of procedures/visits required, MRI, Isolated ARIA-H (asymptomatic), Moderate	[redacted]	[redacted]	[redacted]	[redacted]
Number of procedures/visits required, MRI, Isolated ARIA-H (asymptomatic), Severe	[redacted]	[redacted]	[redacted]	[redacted]
Number of procedures/visits required, MRI, Isolated ARIA-H (symptomatic), Mild	[redacted]	[redacted]	[redacted]	[redacted]
Number of procedures/visits required, MRI, Isolated ARIA-H (symptomatic), Moderate	[redacted]	[redacted]	[redacted]	[redacted]
Number of procedures/visits required, MRI, Isolated ARIA-H (symptomatic), Severe	[redacted]	[redacted]	[redacted]	[redacted]

Number of procedures/visits required, Outpatient visit, ARIA-E (asymptomatic), Mild	[redacted]	[redacted]	[redacted]	[redacted]
Number of procedures/visits required, Outpatient visit, ARIA-E (asymptomatic), Moderate	[redacted]	[redacted]	[redacted]	[redacted]
Number of procedures/visits required, Outpatient visit, ARIA-E (asymptomatic), Severe	[redacted]	[redacted]	[redacted]	[redacted]
Number of procedures/visits required, Outpatient visit, ARIA-E (symptomatic), Mild	[redacted]	[redacted]	[redacted]	[redacted]
Number of procedures/visits required, Outpatient visit, ARIA-E (symptomatic), Moderate	[redacted]	[redacted]	[redacted]	[redacted]
Number of procedures/visits required, Outpatient visit, ARIA-E (symptomatic), Severe	[redacted]	[redacted]	[redacted]	[redacted]
Number of procedures/visits required, Outpatient visit, Isolated ARIA-H (asymptomatic), Mild	[redacted]	[redacted]	[redacted]	[redacted]
Number of procedures/visits required, Outpatient visit, Isolated ARIA-H (asymptomatic), Moderate	[redacted]	[redacted]	[redacted]	[redacted]
Number of procedures/visits required, Outpatient visit, Isolated ARIA-H (asymptomatic), Severe	[redacted]	[redacted]	[redacted]	[redacted]
Number of procedures/visits required, Outpatient visit, Isolated ARIA-H (symptomatic), Mild	[redacted]	[redacted]	[redacted]	[redacted]
Number of procedures/visits required, Outpatient visit, Isolated ARIA-H (symptomatic), Moderate	[redacted]	[redacted]	[redacted]	[redacted]
Number of procedures/visits required, Outpatient visit, Isolated ARIA-H (symptomatic), Severe	[redacted]	[redacted]	[redacted]	[redacted]
Time to worsening HR, OLE, CDR-SB - combined	[redacted]	[redacted]	[redacted]	[redacted]
Time to worsening HR, copy-increments control-based multiple imputation, CDR-SB - combined	[redacted]	[redacted]	[redacted]	[redacted]
Time to worsening HR, Core study, CDR-SB - combined	[redacted]	[redacted]	[redacted]	[redacted]
Proportion of population that are APOE4 homozygous	[redacted]	[redacted]	[redacted]	[redacted]

Proportion of APOE4 homozygous patient that take up genetic counselling	[redacted]	[redacted]	[redacted]	[redacted]
APOE4 Test unit cost	[redacted]	[redacted]	[redacted]	[redacted]
APOE4 Outpatient appointment unit cost	[redacted]	[redacted]	[redacted]	[redacted]
APOE4 Counselling unit cost	[redacted]	[redacted]	[redacted]	[redacted]

Appendix H. Literature searches for the clinical assessment

H.1 Efficacy and safety of the intervention and comparator(s)

H.1.1.1 Objective

The overall objective of the systematic literature review (SLR) was to identify, evaluate, and summarise the clinical efficacy and safety of pharmacological and non-pharmacological treatments used in managing MCI due to AD and mild dementia due to AD.

H.1.1.2 Methods

This literature review is based on a reproducible and validated comprehensive search of the evidence. The SLRs were conducted according to the general recommendations of the Cochrane Handbook for Systematic Reviews of Interventions A full protocol for the literature review was developed prior to the review for detailing the patient population, interventions, and study designs to be included. The SLR was reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (149).

H.1.1.3 Information sources

H.1.1.3.1 Bibliographic databases

Searches were carried out on the following key biomedical databases: Excerpta Medica Database (Embase®), Medical Literature Analysis and Retrieval System Online (MEDLINE®) via embase.com, MEDLINE in-process (searched via PubMed), and Cochrane Central Register of Controlled Trials (CENTRAL) via Cochrane Library.

PubMed was searched to identify In-process citations, which provide records for articles before those records are indexed with MeSH or converted to out-of-scope status. "Ahead of Print" citations that precede the article's final publication in a MEDLINE indexed journal were also searched in PubMed.

An overview of the included bibliographic databases is presented in Table 81. Searches of the electronic databases were performed on May 1st, 2024.

Table 81 Bibliographic databases included in the literature search

Database	Platform/source	Relevant period for the search	Date of search completion
Embase	http://www.embase.com/	Database inception to May 1st, 2024	May 2024
Medline	http://www.embase.com/	Database inception to May 1st, 2024	May 2024

Database	Platform/source	Relevant period for the search	Date of search completion
Medline In-process	https://pubmed.ncbi.nlm.nih.gov/	Database inception to May 1st, 2024	May 2024
CENTRAL	https://www.cochranelibrary.com/	Database inception to May 1st, 2024	May 2024
CDSR	https://www.cochranelibrary.com/	Database inception to May 1st, 2024	May 2024

Abbreviations: CDSR, Cochrane Database of Systematic Reviews; CENTRAL, Cochrane Central Register of Controlled Trials.

H.1.1.3.2 Other sources

Table 82 Other sources included in the literature search

Source name	Location/source	Search strategy	Date of search
N/A	N/A		N/A

H.1.1.3.3 Conference proceedings

Supplementary searches of conference proceedings were reported for the previous four years (2020-23) as listed below and in Table 83.

- AAIC - Annual Alzheimer's Association International Conference.
- EAN – Annual Congress of the European Academy of Neurology.
- ANA – American Neurological Association.
- AAN – American Academy of Neurology.
- ADI - International Conference of Alzheimer's Disease International.
- CTAD- Clinical Trials on Alzheimer's Disease.
- ISPOR – International Society for Pharmacoeconomics and Outcomes Research
- Alzheimer’s Parkinson’s Disease (AD/PD)

Since many conference proceedings are now included within Embase, one reviewer checked the coverage of specific conferences of interest by checking the Embase list of conferences. In addition, because of Cochrane’s Embase project, conference abstracts that are indexed in Embase and are reports of RCTs are now being included in CENTRAL. As per the findings of Cochrane methodology reviews, trials with positive results tended to be published in approximately 4 to 5 years (150, 151), and not all conference presentations are published (150, 151). Furthermore, over one-half of trials reported in conference abstracts never reach full publication (150, 151). Thereby, we restricted the manual handsearching of conference proceedings to the last four years.

Since many conference proceedings were both searched via Embase.com and the respective conference website, Table 83 has been modified to adjust for this.

Table 83 Conference material included in the literature search

Conference	Source of abstracts	Search strategy	Words /terms searched	Date of search
AAIC – Annual Alzheimer's Association International Conference	Embase.com	Indexed (2017, 2018, 2019)	Alzheimer's Disease	01.05.2024
	https://aaic.alz.org/abstracts/abstracts-archive.asp (2023 abstracts were retrieved from [redacted]	Hand search (2020, 2021, 2022, 2023, 2024)	Alzheimer's Disease	01.05.2024
EAN – Annual Congress of the European Academy of Neurology	Embase.com	Indexed (2019, 2020)	Alzheimer's Disease	01.05.2024
	https://www.ean.org/meet/congresses	Hand search (2017, 2018, 2021, 2022, 2023, 2024)	Alzheimer's Disease	01.05.2024
ANA – American Neurological Association	https://myana.org/	Hand search (2017, 2018, 2019, 2020, 2021, 2022, 2023, 2024)	Alzheimer's Disease	01.05.2024
AAN – American Academy of Neurology	Embase.com	Indexed (2017, 2018, 2019 2021, 2022, 2023)	Alzheimer's Disease	01.05.2024
	https://www.aan.com/	Hand search (2020, 2024)	Alzheimer's Disease	01.05.2024
ADI – International Conference of Alzheimer's Disease International	https://adiconference.org/files/general/ADI-2022-Abstract-Book.pdf	Hand search (2017, 2018, 2019, 2020, 2022, 2021. 2023 conference did not happen)	Alzheimer's Disease	01.05.2024
CTAD – Clinical Trials on Alzheimer's Disease	https://www.ctad-alzheimer.com/	Hand search (2017, 2018, 2019, 2020, 2021, 2022. 2023 is not yet published)	Alzheimer's Disease	01.05.2024
ISPOR – International Society for Pharmacoeconomics and Outcomes Research	Embase.com	Indexed (2017, 2018, 2019, 2020, 2021, 2022)	Alzheimer's Disease	01.05.2024
	https://www.ispor.org/heor-resources/presentations-database/search	Hand search (2017, 2018, 2019, 2020,	Alzheimer's	01.05.2024

Conference	Source of abstracts	Search strategy	Words /terms searched	Date of search
		2021, 2022, 2023, 2024)	Disease	
AD/PD – Alzheimer's & Parkinson's Diseases	2021: https://cslide.ctimeetingtech.com/adpd21/attendee/confcal 2022: https://cslide.ctimeetingtech.com/adpd22/attendee/confcal/session/calendar/2022-03-15 2023: https://cslide.ctimeetingtech.com/global_storage/media/content/adpd23/ADPD23_-_Posters_for_website_Mar_29.pdf	Hand search (2020, 2021, 2022, 2023, 2024)	Alzheimer's Disease	01.05.2024

We also conducted bibliographic searching of included studies and relevant literature reviews to supplement the evidence retrieved from the biomedical databases.

H.1.2 Search strategies

The clinical SLR of published evidence used a reproducible and validated search strategy comprised of disease terms, a study design filter, and intervention terms. The research-based adapted search strategies used for identifying studies are based on the filters developed by:

- SIGN (Scottish Intercollegiate Guideline Network; https://www.sign.ac.uk/what-we-do/methodology/search-filters/) and
- CADTH (Canadian Agency for Drugs and Technologies in Health; Search Results - CADTH Search Filters Database - Canadian Agency for Drugs and Technologies in Health).

A combination of Emtree subject headings (Embase®), MeSH (medical subject headings, PubMed®), and free-text terms was used to retrieve all the relevant publications. The specific search strings used in each of the included bibliographic databases are presented in Table 84, Table 85 and Table 86.

Table 84 of search strategy table for Embase® (Database inception to May 1, 2024)

No.	Query	Results
Disease facet (MCI due to AD and mild dementia due to AD)		
1	'Alzheimer disease'/exp	259,985
2	'mild cognitive impairment'/exp	40,877

3	(((mild* OR early* OR preclinical OR 'pre clinical') NEAR/2 ('cognitive impairment' OR 'cognitive impairments' OR 'cognitive impaired' OR 'cognitive dysfunction' OR 'cognitive decline')):ti,ab,de) OR MCI:ti,ab,de	71,170
4	alzheimer*:ti,ab,de	3,11,507
5	#1 OR #2 OR #3 OR #4	3,50,244
Intervention facet		
6	'lecanemab'/syn OR 'BAN2401' OR 'mAb158'	786
7	'donepezil'/syn OR aricept* OR memac* OR memorit* OR eranz*	19,719
8	'rivastigmine'/syn OR rivastigmin* OR exelon* OR prometax*	9,386
9	'galantamine'/syn OR 'galanthamine' OR 'epigalanthamin' OR 'jilkon' OR 'lycoremin' OR 'nivalin' OR 'razadyne' OR 'reminyl' OR galantamin*	10,069
10	'memantine'/syn OR 'ebixa' OR 'axura' OR namenda*	14, 235
11	'cognitive stimulation therapy' OR 'reminiscence therapy' OR 'cognitive rehabilitation' OR 'occupational therapy' OR ((cognitive* OR cognition*) NEAR/2 (stimulat* OR rehab*)) OR reminiscence* OR ((occupation* OR occ) NEAR/2 (therap* OR treat* OR care* OR medicine*))	1,55,111
12	#6 OR #7 OR #8 OR #9 OR #10 OR #11	1,91,840
Study design facet		
13	'randomised controlled trial' OR 'randomized controlled trial' OR 'randomised controlled trials' OR 'randomized controlled trials' OR 'randomisation' OR 'randomization' OR 'rct' OR 'random allocation' OR 'randomly allocated' OR 'allocated randomly' OR 'randomly assigned' OR random* OR 'controlled clinical trial' OR 'placebo' OR 'placebos' OR 'controlled clinical study' OR 'randomised controlled' OR 'randomized controlled' OR ('controlled' NEAR/2 ('study' OR 'design' OR 'trial')) OR 'phase 2 clinical trial' OR 'phase 3 clinical trial' OR 'comparative study' OR 'randomised' OR 'randomized'	12,478,364
14	(allocat* OR assign*) NEAR/2 random*	240,001
15	'double-blind' OR 'double blind' OR 'double-blind method' OR 'double blind method' OR 'double-blind procedure' OR 'double blind procedure' OR 'double-blind study' OR 'double blind study' OR 'single-blind' OR 'single blind' OR 'single-blind method' OR 'single blind method' OR 'single-blind procedure' OR 'single blind procedure' OR 'single-blind study' OR 'single blind study' OR 'cross-over procedure' OR 'cross over procedure' OR ((singl* OR doubl* OR tripl* OR trebl*) NEAR/1 (blind* OR mask* OR dumm*)) OR (('open label' OR 'open-label') NEAR/5 ('study' OR 'studies' OR trial*)) OR ('parallel' NEXT/1 'group') OR 'crossover' OR 'cross-over' OR 'cross over'	559,529
16	#13 OR #14 OR #15	12,535,126
17	'case study'/de OR 'case report' OR 'abstract report'/de OR 'letter'/de	4,296,884
18	#16 NOT #17	12,300,011
Combined facet with limits		
19	#5 AND #12 AND #18	10,858
20	#19 AND [animals]/lim NOT ([humans]/lim AND [animals]/lim)	2,263
21	#19 AND ([conference review]/lim OR [editorial]/lim OR [letter]/lim OR [note]/lim OR [review]/lim OR [short survey]/lim)	1,992

22	#20 OR #21	4,240
23	#19 NOT #22	6,618
24	#19 NOT #22 AND [english]/lim	6,427

Table 85 of search strategy table for Cochrane Library (Database inception to May 1, 2024)

No.	Query	Results
Disease facet (MCI due to AD and mild dementia due to AD)		
1	MeSH descriptor: [Alzheimer Disease] explode all trees	5,334
2	MeSH descriptor: [Cognitive dysfunction] explode all trees	3,988
3	(((mild* OR early* OR preclinical OR “pre clinical”) NEAR/2 (“cognitive impairment” OR “cognitive impairments” OR “cognitive impaired” OR “cognitive dysfunction” OR “cognitive decline”)):ti,ab,kw) OR MCI:ti,ab,kw	6,349
4	alzheimer*:ti,ab,kw	14,496
5	#1 OR #2 OR #3 OR #4	20,646
Intervention facet		
6	'lecanemab' OR 'BAN2401' OR 'mAb158'	76
7	MeSH descriptor: [donepezil] explode all trees	753
8	aricept* OR memac* OR memorit* OR eranz*	190
9	MeSH descriptor: [rivastigmine] explode all trees	331
10	rivastigmin* OR exelon* OR prometax*	848
11	MeSH descriptor: Memantine] explode all trees	525
12	“ebixa” OR “axura” OR namenda*	81
13	MeSH descriptor: [galantamine] explode all trees	289
14	“galanthamine” OR “epigalanthamin” OR “jilkon” OR “lycoremin” OR “nivalin” OR “razadyne” OR “reminyl” OR galantamin*	736
15	“cognitive stimulation therapy” OR “reminiscence therapy” OR “cognitive rehabilitation” OR “occupational therapy” OR ((cognitive* OR cognition*) NEAR/2 (stimulat* OR rehab*)) OR reminiscence* OR ((occupation* OR occ) NEAR/2 (therap* OR treat* OR care* OR medicine*))	11,531
16	#6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15	14,244
Study design facet		
17	"randomised controlled trial" OR "randomized controlled trial" OR "randomised controlled trials" OR "randomized controlled trials" OR "randomisation" OR "randomization" OR "rct" OR "random allocation" OR "randomly allocated" OR "allocated randomly" OR "randomly assigned" OR random* OR "controlled clinical trial" OR "placebo" OR "placebos" OR "controlled clinical study" OR "randomised controlled" OR "randomized controlled" OR ("controlled" NEAR/2 ("study" OR "design" OR "trial")) OR "phase 2 clinical trial" OR "phase 3 clinical trial" OR "comparative study" OR "randomised" OR "randomized"	1,587,012
18	(allocat* OR assign*) NEAR/2 random*	273,208
19	"double-blind" OR "double blind" OR "single-blind" OR "single blind"	443,190

No.	Query	Results
20	"double blind method" OR "double blind procedure" OR "double blind study" OR "single blind method" OR "single blind procedure" OR "single blind study" OR "cross over procedure"	305,567
21	((singl* OR doubl* OR tripl* OR trebl*) NEAR/1 (blind* OR mask* OR dumm*)) OR ((“open label” OR “open-label”) NEAR/5 (“study” OR “studies” OR trial*))	532,650
22	("parallel" NEXT/1 "group") OR "crossover" OR "cross-over" OR "cross over"	181,382
23	#17 OR #18 OR #19 OR #20 OR #21 OR #22	1,627,329
24	"case study" OR "case report" OR "abstract report" OR "letter"	33,045
25	#23 NOT #24	1,597,197
Combined facet with limits		
26	#5 AND #16 AND #25	2,371
27	#26 in Cochrane Reviews and Trials	2,368
28	#27 NOT (pubmed OR embase):an	778

Table 86 of search strategy table for PubMed® (Database inception to May 1, 2024)

No.	Query	Results
Disease facet (MCI due to AD and mild dementia due to AD)		
1	"Alzheimer Disease"	133,149
2	"Mild cognitive impairment"	26,700
3	(mild* OR early* OR preclinical OR "pre clinical") AND ("cognitive impairment" OR "cognitive impairments" OR "cognitive impaired" OR "cognitive dysfunction" OR "cognitive decline")	51,909
4	MCI[Title/Abstract]	24,940
5	alzheimer*[Title/Abstract]	200,563
6	#1 OR #2 OR #3 OR #4 OR #5	250,192
Intervention facet		
7	‘‘lecanemab’’ OR “BAN2401” OR “mAb158”	301
8	"Donepezil" OR aricept* OR memac* OR memorit* OR eranz*	5,269
9	“Rivastigmine” OR rivastigmin* OR exelon* OR prometax*	2,345
10	“Memantine” OR “ebixa” OR “axura” OR namenda*	4,617
11	"Galantamine" OR “galanthamine” OR “epigalanthamin” OR “jilkon” OR “lycoremin” OR “nivalin” OR “razadyne” OR “reminyl” OR galantamin*	3,005
12	“cognitive stimulation therapy” OR “reminiscence therapy” OR “cognitive rehabilitation” OR “occupational therapy” OR ((cognitive* OR cognition*) AND (stimulat* OR rehab*)) OR reminiscence* OR ((occupation* OR occ) AND (therap* OR treat* OR care* OR medicine*))	357,857
13	#7 OR #8 OR #9 OR #10 OR #11 OR #12	369,950
Study design facet		
14	"randomised controlled trial" OR "randomized controlled trial" OR "randomised controlled trials" OR "randomized controlled trials" OR "randomisation" OR "randomization" OR "rct" OR "random allocation"	3,822,524

No.	Query	Results
	OR "randomly allocated" OR "allocated randomly" OR "randomly assigned" OR random* OR "controlled clinical trial" OR "placebo" OR "placebos" OR "controlled clinical study" OR "randomised controlled" OR "randomized controlled" OR ("controlled" AND ("study" OR "design" OR "trial")) OR "phase 2 clinical trial" OR "phase 3 clinical trial" OR "comparative study" OR "randomised" OR "randomized"	
15	(allocat* OR assign*) AND random*	347,647
16	"double-blind" OR "double blind" OR "double-blind method" OR "double blind method" OR "double-blind procedure" OR "double blind procedure" OR "double-blind study" OR "double blind study" OR "single-blind" OR "single blind" OR "single-blind method" OR "single blind method" OR "single-blind procedure" OR "single blind procedure" OR "single-blind study" OR "single blind study" OR "cross-over procedure" OR "cross over procedure" OR ((singl* OR doubl* OR tripl* OR trebl*) AND (blind* OR mask* OR dumm*)) OR (("open label" OR "open-label") AND ("study" OR "studies" OR trial*)) OR ("parallel" AND "group") OR "crossover" OR "cross-over" OR "cross over"	470,499
17	#14 OR #15 OR #16	3,934,450
18	"case study" OR "case report" OR "abstract report" OR "letter"	1,845,502
19	#17 NOT #18	3,863,275
Combined facet with limits		
20	#6 AND #13 AND #19	4,471
21	(#20 AND (inprocess[sb] OR pubstatusaheadofprint))	33

H.1.3 Systematic selection of studies

H.1.3.1 Eligibility criteria

Selection of studies for inclusion was determined using the PICOS framework (152). To be included in this review, trials had to meet the following pre-defined eligibility criteria of clinical review as specified in Table 87.

Table 87 Inclusion and exclusion criteria used for assessment of studies

Clinical effectiveness	Inclusion criteria	Exclusion criteria	Changes, local adaption
Population	Disease		
	• Patients with MCI due to AD • Patients with mild dementia due to AD • Patients with MCI due to AD and mild dementia due to AD (both patient cohorts included) • Patients with MCI due to unknown reasons will be included only if mild dementia due to	• Patients with MCI due to unknown reasons • Patients with MCI due to non-AD (not unknown) reasons • Patients with preclinical AD • Patients with moderate dementia due to AD • Patients with severe dementia due to AD	• No change

	AD is also presented in the study (this indicates AD could have been included among the unknown reasons for MCI)	• Patients with severity not reported
		• Patients with a specific type of dementia other than AD, e.g., Parkinson's, vascular dementia, or frontotemporal dementia
		• Patients with mixed disease were included if the study indicated the subgroup analysis of the population of interest, i.e., MCI due to AD or mild dementia due to AD. The detailed evaluation of subgroup analysis was conducted at the full-text screening stage
		• Patients with mixed disease staging (based on severity, e.g., mild to moderate) were included if the study indicated the subgroup analysis of the population of interest, i.e., MCI or mild dementia due to AD
		  ○ Patients with mild to moderate dementia due to AD with no subgroup analysis for mild dementia due to AD were excluded
		  ○ Patients with mild to severe dementia due to AD with no subgroup analysis for mild dementia due to AD were excluded

		• Patients with MCI due to AD (+ other reasons) with no subgroup analysis for MCI due to AD were excluded	
	Age		
	Adult (≥18 years) patients	Studies evaluating children	
	Race		
	No restriction	Not applicable	No change
	Gender		
	No restriction	Not applicable	No change
Intervention	• Lecanemab • Donepezil • Rivastigmine • Galantamine • Memantine (Only to be considered when studies evaluating memantine also evaluate any AChE inhibitor or listed non-pharmacological therapy) • Cognitive stimulation therapy • Reminiscence therapy • Cognitive rehabilitation • Occupational therapy	• Studies evaluating memantine alone • Other non-pharmacological interventions (that are not recommended), e.g., acupuncture, vitamin E supplements, ginseng, herbal formulations, interpersonal therapy, magnetic stimulation	No change
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.	NA	Narrowed down to only include placebo/best supportive care, and active symptomatic treatments, i.e., donepezil, rivastigmine, galantamine, and memantine in line with current Danish clinical practice

Outcomes	• CDR-SB • CDR global score • ADCOMS • 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 (edema or effusions), ARIA-H (cerebral microhemorrhages, cerebral macrohemorrhages, or superficial siderosis), headache, fall, diarrhoea, dizziness, infusion-related reactions, and skin rash • Study withdrawals and treatment discontinuations	Studies not reporting relevant outcomes of interest were excluded	No change
Study design/publication type	• 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	• No change
	Peer-reviewed journal articles and conference abstracts (searched for the previous five years, 2020-2024)	Editorials, newspaper articles, book sections, expert opinion or commentary, trial protocols, and reviews	No change

Language restrictions	Studies with full texts published in the English language only	Studies with full texts published in the non-English language	No change

Abbreviations: AChE, Acetylcholinesterase; AD, Alzheimer's disease; ADAS-Cog, Alzheimer's Disease Assessment Scale - Cognitive Section; ADCOMS, Alzheimer's Disease Composite Score; ADCS-ADL, Alzheimer's Disease Cooperative Study - Activities of Daily Living Scale; ADCS-ADL-MCI, Alzheimer's Disease Cooperative Study - Activities of Daily Living for Mild Cognitive Impairment Scale; AE, Adverse event; ARIA, Amyloid-related imaging abnormality; CDR, Clinical Dementia Rating; CDR-SB, Clinical Dementia Rating-Sum of Boxes; MCI, Mild cognitive impairment; MMSE, Mini-Mental State Examination; NA, Not applicable; PET, Positron emission tomography; RCT, Randomised controlled trial; SUVR, Standardized uptake value ratio.

Additionally, RCTs published as conference abstracts (only) before 2020 were excluded, as they are less likely to be published as a complete manuscript journal publication after a gap of 4-5 years. Likewise, RCTs evaluating relevant treatments (listed above) in an add-on/background/concomitant manner were excluded, as such treatment combinations are not of interest as the primary set of randomised treatments are non-relevant.

H.1.3.2 Study selection process

H.1.3.2.1 Global SLR

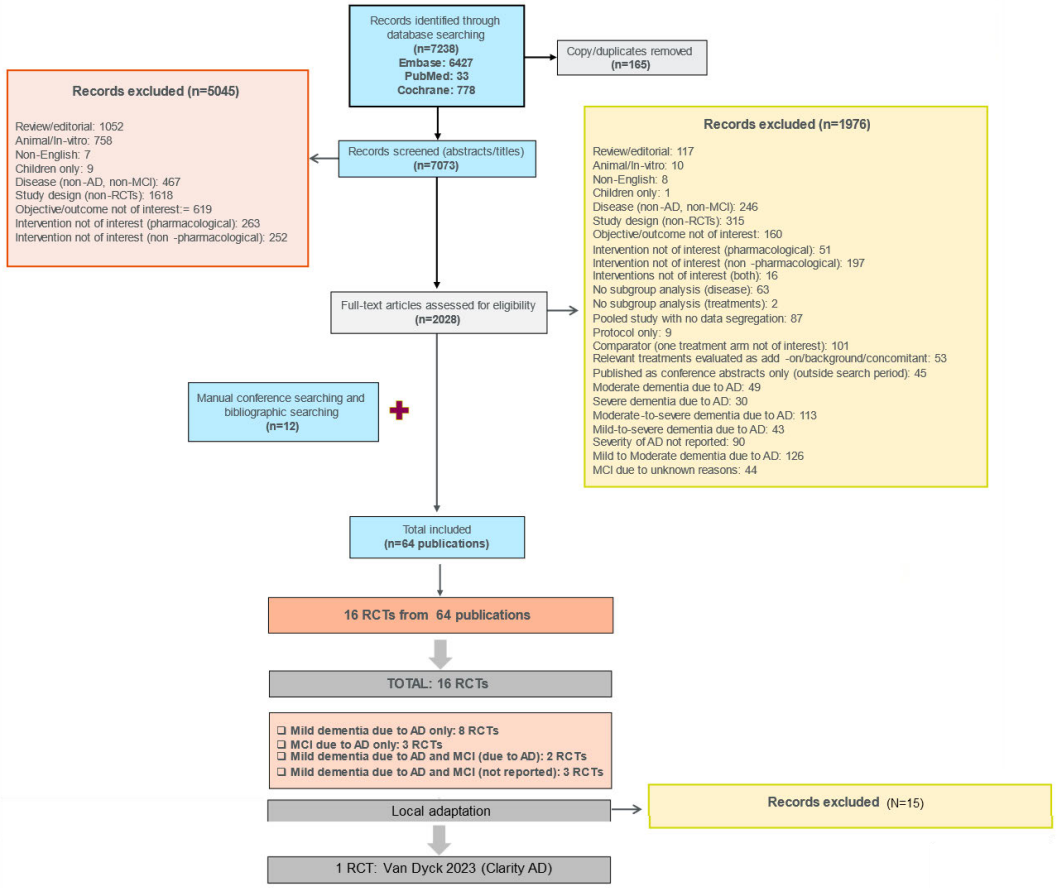
Initial screening of the retrieved citations was undertaken based on the title and abstract. Citations that did not match the eligibility criteria were excluded at this 'first pass' stage. If there was lack of clarity on whether citations were eligible for the review due to limited information in the abstract, these citations were included for 'second pass' stage. Two independent reviewers screened all citations and full text papers and any discrepancies in their decisions were resolved by a third reviewer. Citation duplicates (due to the overlap in the coverage of the databases) were also excluded at this stage. Upon acceptance during the initial screening, full-text copies of all references that could potentially meet the eligibility criteria were retrieved.

The full-text publications of all citations of potential interest were then screened for inclusion. Two independent reviewers screened all citations and full text papers and any discrepancies in their decisions were resolved by a third reviewer. Citations that did not match the eligibility criteria were excluded at this 'second-pass' stage. At the full text screening stage, if there was lack of clarity on whether the publication met the eligibility criteria, these citations were excluded. Full-text screening was followed by linking of multiple publications. Studies meeting the eligibility criteria at the second screening stage were extracted.

The literature search yielded 7,328 separate references. Due to the overlap of coverage between the databases, 165 of the abstracts were duplicates. Following the first pass of the publications, 2,028 potentially relevant publications were identified. Full-text reports of these publications were retrieved for a more detailed evaluation. In total, 64 publications were identified, including 12 publications retrieved through the searching of conference proceedings and bibliographies of relevant studies.

Since some studies were reported in several articles and conference abstracts, the comprehensive search of studies for the review identified multiple reports from relevant studies. So, upon linking together multiple reports of the same study, we identified 1 RCT (Van Dyck 2023). The study selection process of the SLR is detailed in the PRISMA flow-chart presented in Figure 31

Figure 31 PRISMA flow chart of the global SLR



Abbreviations: AD: Alzheimer's disease; MCI: Mild cognitive impairment; RCT: Randomised controlled trial

H.1.3.3 Summary of included studies

1 RCT was identified that reported the efficacy and/or safety data of the required treatments (Van Dyck 2023). A summary of the key study and patient characteristics is provided in Table 88 below.

Table 88 Overview of study design for studies included in the analyses

Study/ID	Aim	Study design	Patient population	Interven-tion and compara-tor (sample size (n))	Primary outcome and follow-up period	Secondary outcome and follow-up period
Van Dyck 2023 (Clarity AD)	Efficacy and safety	Phase III, double-blind, multicentre international	Mild dementia due to AD and MCI due to AD	Lecanemab (n = 898)	CDR-SB (78 weeks)	• ADAS-cog14 score, ADCOMS score, ADCS-MCI-ADL score. • Amyloid burden on PET as measured in centiloids (with either florbetaben, florbetapir, or flutemetamol tracers) in a substudy.
				Placebo (n = 897)		
				Placebo (n = 530)		
				MCI: Control (n = 12)		
				Mild AD: Cognitive intervention (n = 8)		
				Mild AD: Control (n = 7)		

Abbreviations: Alzheimer's disease; ADAS-cog, Alzheimer's disease assessment scale-cognitive subscale; ADCOMS, Alzheimer's Disease Composite Score; CDR-SB, Clinical dementia rating scale-sum of boxes; PET, Positron emission tomography.

H.1.3.4 Excluded full text references

A list of excluded studies during the local adaptation, including reason for exclusion is provided in Table 89.

Table 89 Overview of excluded studies

Reference	Reason for exclusion
Seltzer B., Zolnouni P., Nunez M., Goldman R., Kumar D., Ieni J., Richardson S. (2004). Efficacy of donepezil in early-stage Alzheimer disease: A randomized placebo-controlled trial. Archives of Neurology 61(12): 1852-56.	Not relevant treatment
Tariot, P.N., Solomon, P.R., Morris, J.C., Kershaw, P., Ding, C (2000). A 5-month, randomized, placebo-controlled trial of galantamine in AD. The Galantamine USA-10 Study Group. Neurology 54(12): 2269-2276.	Not relevant treatment

Silva A.R., Pinho M.S., MacEdo L., Moulin C., Caldeira S., Firmino H. (2017). It is not only memory: Effects of sensecam on improving well-being in patients with mild Alzheimer disease. International Psychogeriatrics 29(5): 741-54	Not relevant treatment
Tsantali E., Economidis D., Rigopoulou S. (2017). Testing the benefits of cognitive training vs. cognitive stimulation in mild Alzheimer's disease: A randomised controlled trial. Brain Impairment 18(2): 188-196.	Not relevant treatment
Kadir A., Darreh-Shori T., Almkvist O., Wall A., Grut M., Strandberg B., Ringheim A., B. Eriksson, Blomquist G., Långström B., Nordberg A. (2008). PET imaging of the in vivo brain acetylcholinesterase activity and nicotine binding in galantamine-treated patients with AD. Neurobiology of Aging 29(8): 1204-1217.	Not relevant treatment
Kim D. (2020). The Effects of a Recollection-Based Occupational Therapy Program of Alzheimer's Disease: A Randomized Controlled Trial. Occupational therapy international: 6305727.	Not relevant treatment
Bottino C.M.C., Carvalho I.A.M., Alvarez A.M.M.A., Avila R., Zukauskas P.R., Bustamante S.E.Z., Andrade F.C., Hototian S.R., Saffi F., Camargo C.H.P. (2005). Cognitive rehabilitation combined with drug treatment in Alzheimer's disease patients: A pilot study. Clinical Rehabilitation 19(8): 861-869.	Not relevant treatment
Brueggen K., Kasper E., Ochmann S., Pfaff H., Webel S., Schneider W., Teipel S. (2017). Cognitive Rehabilitation in Alzheimer's Disease: A Controlled Intervention Trial. Journal of Alzheimer's Disease 57(4): 1315-1324.	Not relevant treatment

H.1.4 Quality assessment

Included studies were critically appraised using the Cochrane risk of bias assessment tool. Studies were objectively assessed for internal validity using the risk of bias 2.0. A summary of the risk of bias assessment of studies including patients with MCI due to AD or MCI due to unknown reasons and mild dementia due to AD is provided in Table 90.

Table 90: Summary of the risk of bias assessment

Study	Risk of bias domain				
	D1	D2	D3	D4	D5
Van Dyck 2023	Low	Low	Low	Low	Low

Note: D1, Bias araising from the randomisation process; D2, Bias due to deviations from the Intended Interventions; D3, Bias due to missing outcome data; D4, Bias in the measurement of the outcome; D5, Bias in the selection of the reported result.

The critical appraisal of this trial showed that it was of high quality with low risk of bias on all domains.

H.1.5 Unpublished data

N/A

Appendix I. Literature searches for health-related quality of life

I.1 Health-related quality-of-life search

I.1.1.1 Objective

The overall objective of this SLR was to identify the health state utility data associated with all stages of AD (including MCI due to AD and mild-moderate-severe dementia due to AD).

A global SLR was used to select the relevant information for the Danish adaptation.

I.1.1.2 Methods

This literature review is based on a reproducible and validated comprehensive search of the evidence. The SLRs were conducted according to the general recommendations of the Cochrane Handbook for Systematic Reviews of Interventions A full protocol for the literature review was developed prior to the review for detailing the patient population, interventions, and study designs to be included. The SLR was reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (149).

I.1.1.3 Information sources

I.1.1.3.1 Bibliographical databases

Medical Literature Analysis and Retrieval System Online (MEDLINE®), Excerpta Medica Database (Embase®), and the Cochrane Library. The Cochrane Database of Systematic Reviews (CDSR) and Cochrane Controlled Register of Trials (CENTRAL) were indexed in Cochrane Library and were not searched individually. In-process citations, which provide records for articles before those records are indexed with MeSH (Medical Subject Headings), were searched using PubMed. The Ahead of Print Citations that appeared on the web prior to their publication in final or print format were also searched using PubMed. One additional primary database (recommended by NICE), i.e., PsycInfo was searched using the Ovid interface (APA PsycInfo 1987 to September 1, 2023).

Table 91 Bibliographic databases included in the literature search

Database	Platform	Relevant period for the search	Date of search completion
Embase	Embase.com	January 1990 to April 2024	01.05.2024
Medline	Ovid	January 1990 to April 2024	01.05.2024
Cochrane Library	cochranelibrary.com	January 1990 to April 2024	01.05.2024

Database	Platform	Relevant period for the search	Date of search completion
PsycINFO	apa.org/pubs/databases/psycinfo	January 1990 to April 2024	01.05.2024

I.1.1.3.2 Other sources

OpenGrey (system for information on grey literature in Europe) and TRIP (Turning Research in Practice), were searched as supplementary sources to avoid missing relevant evidence.

Table 92 Other sources included in the literature search

Source name	Location/source	Search strategy	Date of search
TRIP		Keywords: (dementia OR alzheimer) AND (qol OR hrqol OR 'quality of life' OR 'health-related quality of life' OR utility)	01.05.2024
OpenGray		Keywords: (dementia OR alzheimer) AND (qol OR hrqol OR 'quality of life' OR 'health-related quality of life' OR utility)	01.05.2024

I.1.1.3.3 Conference proceedings

Supplementary searches of conference proceedings were reported for the previous five years (2020-24) as listed in Table 93. Since many conference proceedings are now included within Embase, one reviewer checked the coverage of specific conferences of interest by checking the Embase list of conferences (https://www.elsevier.com/solutions/embase-biomedical-research/coverage-and-content). In addition, because of Cochrane's Embase project, conference abstracts that are indexed in Embase and are reports of RCTs are now being included in CENTRAL. As per the findings of Cochrane methodology reviews, trials with positive results tended to be published in approximately 4 to 5 years, and not all conference presentations are published. Furthermore, over one-half of trials reported in conference abstracts never reach full publication. Thereby, we restricted the manual handsearching of conference proceedings to the last five years.

Table 93 Conference material included in the literature search

Conference	Source of abstracts	Search strategy	Words/terms searched	Date of search
AAIC - Annual Alzheimer's Association International Conference.	Conference website (https://aaic.alz.org/abstracts/abstracts-archive.asp) and Embase	Hand search	N/A	01.05.2024

Conference	Source of abstracts	Search strategy	Words/terms searched	Date of search
EAN – Annual Congress of the European Academy of Neurology	[redacted] and Embase	Hand search	N/A	01.05.2024
ANA – American Neurological Association	https://myana.org/	Hand search	N/A	01.05.2024
AAN – American Academy of Neurology	[redacted] and Embase	Hand search	N/A	01.05.2024
ADI - International Conference of Alzheimer's Disease International	https://adiconference.org/files/general/ADI-2022-Abstract-Book.pdf	Hand search	N/A	01.05.2024
CTAD- Clinical Trials on Alzheimer's Disease	https://www.ctad-alzheimer.com/ and Embase	Hand search	N/A	01.05.2024
ISPOR – International Society for Pharmacoeconomics and Outcomes Research	[redacted] and Embase	Hand search	N/A	01.05.2024
Alzheimer's Parkinson's Disease (AD/PD)	2021: https://cslide.ctimeetingtech.com/adpd21/attendee/confcal 2022: https://cslide.ctimeetingtech.com/adpd22/attendee/confcal/session/calendar/2022-03-15 2023: https://cslide.ctimeetingtech.com/global_storage/media/content/adpd23/ADPD23_-Posters for website Mar 29.pdf 2024: https://cslide.ctimeetingtech.com/adpd24/attendee/confcal/session/list	Hand search	N/A	01.05.2024

Abbreviations: N/A = Not applicable

I.1.2 Search strategies

The primary search was conducted in 2017, and 5 updates were conducted in 2019, 2020, 2021, 2023, and 2024. The updated search was conducted on May the 1st, 2021.

As recommended by various HTA agencies such as NICE (153), SMC (154), G-BA (155) and for comprehensiveness of the data collection, search strategies were developed through the combination of free text words, indexing terms and by using Boolean terms (e.g. 'and',

'or') to the terms relevant to disease area and study designs. Outcome measures were not included in the search strategy but rather were incorporated into the inclusion/exclusion criteria of the SLRs. The search strings were appropriately modified to fit each database-specific syntax and presented in Table 94 to Table 98, while the inclusion and exclusion criteria are described in section I.1.3

Table 94 Search strategy for Embase.com (Embase + MEDLINE)

No.	Query	Results
#1	MeSH descriptor: [Dementia] explode all trees	277,451
#2	MeSH descriptor: [Cognitive Dysfunction] explode all trees	73,077
#3	(dementia* OR alzheimer*):ti	200,243
#4	((mild* OR early* OR preclinical OR pre-clinical) NEAR/2 ("cognitive impair" OR "cognitive dysfunction" OR "cognitive decline")):ti	16,191
#5	#1 OR #2 OR #3 OR #4	362,427
#6	MeSH descriptor: [Quality of Life] explode all trees	146,204
#7	("quality of life" OR "quality of wellbeing" OR "quality of well-being"):ti	138,814
#8	(qol OR hqol OR hrqol OR hrql OR hr-qol OR hr-ql OR euroqol OR "euro qol" OR eq5d OR eq-5d OR eq-vas OR vas OR whoqol OR "who qol" OR reqol*):ti,ab,kw	264,746
#9	(sf6 OR sf6d OR sf12 OR sf16 OR sf20 OR sf36):ti,ab,kw	56,266
#10	((sf OR shortform OR short-form) NEXT/1 ("6" OR 6d OR "12" OR "16" OR "20" OR "36" OR six OR twelve OR sixteen OR twenty OR thirtysix OR "thirty six")):ti	63,535,
#11	(icepop OR icecap* OR "duke health profile" OR dhp OR "core outcome measure" OR "core om"):ti,ab,kw	5,314
#12	(aaiqol OR aai-qol OR cdqlp OR qolas OR qolad OR qol-ad OR qold OR dqol OR demqol OR adrql OR adrqol OR oqold OR oqolda OR seiqol OR rsoc-qol OR qualid OR qualidem OR qwb-sa OR hsq-12 OR zbi OR zarit OR ces-d OR "activity and affect indicator" OR dcm OR pwbcip OR pwb-cip OR npi-d OR ham-d OR basquid OR basqid OR stai OR stai-5 OR bdi OR gds OR gps OR hui OR hui-ii OR hui-iii OR isd OR pds OR pes-ad OR pesad OR pes-ad-aes OR pesadaes OR ghq OR cas OR cbs OR qwb OR cbi OR bsi OR srb OR phq-9):ti,ab,kw	219,672
#13	("modified coop" OR "modified wonca" OR "psychological well-being in cognitively impaired persons"):ti,ab,kw	46
#14	MeSH descriptor: [Patient Satisfaction] this term only	33,157
#15	MeSH descriptor: [Personal Satisfaction] explode all trees	15,230
#16	((life OR patient* OR carer? OR caregiver? OR spous* OR wife OR wives OR husband?) NEXT/1 satisfaction):ti,ab,kw	12,308
#17	((life OR patient* OR carer? OR caregiver? OR spous* OR wife OR wives OR husband?) NEXT/1 (experience? OR preference? OR perspective?)):ti,ab,kw	31,117
#18	(wellbeing OR well-being):ti	313
#19	((life OR patient* OR carer? OR caregiver? OR spous* OR wife OR wives OR husband?) NEXT/1 (experience? OR preference? OR perspective?)):ti,ab,kw	79,377

#20	“caregiver time”:ti,ab,kw	1,064,159
#21	((carer? OR caregiver? OR care OR spous* OR wife OR wives OR husband?) NEAR/2 (burden* OR cost?)):ti,ab,kw	501,836
#22	“burden interview”:ti,ab,kw	9,0461
#23	“value of life”:ti,ab,kw	6,830
#24	MeSH descriptor: [Activities of Daily Living] explode all trees	1,346,069
#25	“activities of daily living” OR acdl OR "funtional status":ti,ab,kw	141
#26	MeSH descriptor: [Quality-Adjusted Life Years] explode all trees	4,539
#27	(“quality adjusted life years” OR "disability adjusted life years" OR qaly? OR daly? OR qald OR qale OR qtime OR qualy):ti,ab,kw	5,957
#28	MeSH descriptor: [Health Status] explode all trees	1
#29	MeSH descriptor: [Sickness Impact Profile] explode all trees	109
#30	(“standard gamble” OR "time trade off" OR "utility index" OR "visual analog"):ti,ab,kw	17,194
#31	(“health utilit” OR disutilit* OR "utility value"):ti,ab,kw	4,199
#32	'quality adjusted life year'/mj	1,959
#33	'quality adjusted life years':ti OR 'disability adjusted life years':ti OR qaly?:ti OR daly?:ti OR qald:ti OR qale:ti OR qtime:ti OR qualy:ti	1,162
#34	'health status'/mj	40,051
#35	'sickness impact profile'/mj	720
#36	'standard gamble':ti,ab OR 'time trade off':ti,ab OR 'utility index':ti,ab OR ((visual NEXT/1 analog*):ti,ab)	123,026
#37	((health NEXT/1 utilit*):ti,ab) OR disutilit*:ti,ab OR ((utility NEXT/1 value?):ti,ab)	8,846
#38	'health status':ti	15,130
#39	'carer wellbeing and support question*':ti,ab OR 'carer well-being and support question*':ti,ab OR 'impact of alzheimers disease on the caregiver questionnaire*':ti,ab OR iadcq:ti,ab OR 'caregiver wellbeing scale*':ti,ab OR 'caregiver well-being scale*':ti,ab OR 'caregiver-targeted quality-of-life measure*':ti,ab OR cgqol:ti,ab OR cqol:ti,ab OR 'caregiver quality of life scale*':ti,ab OR 'caring questionnaire*':ti,ab OR 'caregiver quality of life questionnaire*':ti,ab OR 'ascot-carer*':ti,ab	194
#40	#6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39	70,2933
#41	#5 AND #40	12,115
#42	(demqol*:ti,ab OR 'ad 5d':ti,ab) OR (alzheimer*:ti,ab AND disease:ti,ab AND five:ti,ab AND dimension*:ti,ab) OR ('dementia specific':ti,ab AND quality:ti,ab AND of:ti,ab AND life:ti,ab)	539
#43	#41 OR #42	12,430
#44	'caregiver'/mj OR carer?:ti OR caregiver?:ti	44,916
#45	euroqol:ti,ab OR 'euro qol':ti,ab OR eq5d:ti,ab OR 'eq-5d':ti,ab OR 15d:ti,ab OR “15 d”:ti,ab OR '15 dimension':ti,ab OR aqol:ti,ab OR (((sf OR shortform OR 'short-form') NEAR/1 (6d OR '6-d' OR '6 dimension')):ti,ab) OR 'health utilit* ind*':ti,ab OR hui2:ti,ab OR 'hui 2':ti,ab OR hui3:ti,ab OR	90,113

	'hui 3':ti,ab OR 'quality of wellbeing':ti,ab OR 'quality of well-being':ti,ab OR qwb:ti,ab OR sf36:ti,ab OR (((sf OR shortform OR 'short-form') NEAR/1 ('36' OR thirtysix OR 'thirty six')):ti,ab) OR carerqol:ti,ab OR 'icecap-o':ti,ab	
#46	#44 AND #45 AND #5	136
#47	#43 OR #46 OR #25	12,532
#48	'phase 1 clinical trial'/de OR 'case report'/de OR editorial:it OR letter:it OR note:it OR press:it OR 'case report':ti OR 'case study':ti OR letter?:ti OR editorial:ti	6,304,009
#49	'grounded theory'/de OR 'qualitative research'/exp OR 'qualitative research':ti,ab OR 'qualitative study':ti,ab OR ((qualitative NEXT/1 interview*):ti,ab) OR 'grounded theory':ti,ab OR hermeneutic*:ti,ab	182,040
#50	#48 OR #49	6,476,055
#51	#47 NOT #50	11,475
#52	#51 AND [english]/lim AND [1-1-1990]/sd NOT [27-6-2021]/sd	10,549
#53	#51 AND [english]/lim AND [27-06-2021]/sd NOT [31-08-2023]/sd	1,844
#54	#51 AND [english]/lim AND [1-09-2023]/sd NOT [1-05-2024]/sd	516
#55	#52 OR #53 OR #54	12,909
#56	‘zarit’ OR ‘zarit burden interview’ OR ‘zarit caregiver burden interview’	2,978
#57	(#5 AND #55) NOT #50 AND [english]/lim AND [1-1-1990]/sd NOT [31-08-2023]/sd	869
#58	(#5 AND #56) NOT #50 AND [english]/lim AND [1-9-2023]/sd NOT [1-05-2024]/sd	37
#59	#55 OR #57 OR 58	13,041

Table 95 Search strategy for Cochrane Library (CDSR + CENTRAL)

No.	Query	Results
1	MeSH descriptor: [Dementia] explode all trees	9,439
2	MeSH descriptor: [Cognitive Dysfunction] explode all trees	3,988
3	(dementia* OR alzheimer*):ti	15,662
4	((mild* OR early* OR preclinical OR pre-clinical) NEAR/2 (“cognitive impair” OR “cognitive dysfunction” OR “cognitive decline”)):ti	104
5	#1 OR #2 OR #3 OR #4	21,270
6	MeSH descriptor: [Quality of Life] explode all trees	43,875
7	(“quality of life” OR "quality of wellbeing" OR "quality of well-being"):ti	24,909
8	(qol OR hqol OR hrqol OR hrql OR hr-qol OR hr-ql OR euroqol OR “euro qol” OR eq5d OR eq-5d OR eq-vas OR vas OR whoqol OR “who qol” OR reqol*):ti,ab,kw	95,100
9	(sf6 OR sf6d OR sf12 OR sf16 OR sf20 OR sf36):ti,ab,kw	2,033
10	((sf OR shortform OR short-form) NEXT/1 ("6" OR 6d OR "12" OR "16" OR "20" OR "36" OR six OR twelve OR sixteen OR twenty OR thirtysix OR “thirty six”)):ti	28,444

11	(icepop OR icecap* OR "duke health profile" OR dhp OR "core outcome measure" OR "core om"):ti,ab,kw	417
12	(aaiqol OR aai-qol OR cdqlp OR qolas OR qolad OR qol-ad OR qold OR dqol OR demqol OR adrql OR adrqol OR oqold OR oqolda OR seiqol OR rsoc-qol OR qualid OR qualidem OR qwb-sa OR hsq-12 OR zbi OR zarit OR ces-d OR "activity and affect indicator" OR dcm OR pwbcip OR pwb-cip OR npi-d OR ham-d OR basquid OR basqid OR stai OR stai-5 OR bdi OR gds OR gps OR hui OR hui-ii OR hui-iii OR isd OR pds OR pes-ad OR pesad OR pes-ad-aes OR pesadaes OR ghq OR cas OR cbs OR qwb OR cbi OR bsi OR srb OR phq-9):ti,ab,kw	41,450
13	(“modified coop” OR "modified wonca" OR "psychological well-being in cognitively impaired persons"):ti,ab,kw	1
14	MeSH descriptor: [Patient Satisfaction] this term only	14,401
15	MeSH descriptor: [Personal Satisfaction] explode all trees	1,532
16	((life OR patient* OR carer? OR caregiver? OR spous* OR wife OR wives OR husband?) NEXT/1 satisfaction):ti,ab,kw	39,595
17	((life OR patient* OR carer? OR caregiver? OR spous* OR wife OR wives OR husband?) NEXT/1 (experience? OR preference? OR perspective?)):ti,ab,kw	20,687
18	(wellbeing OR well-being):ti	3,941
19	((life OR patient* OR carer? OR caregiver? OR spous* OR wife OR wives OR husband?) NEXT/1 (experience? OR preference? OR perspective?)):ti,ab,kw	20,687
20	“caregiver time”:ti,ab,kw	83
21	((carer? OR caregiver? OR care OR spous* OR wife OR wives OR husband?) NEAR/2 (burden* OR cost?)):ti,ab,kw	15,206
22	“burden interview”:ti,ab,kw	379
23	“value of life”:ti,ab,kw	61
24	MeSH descriptor: [Activities of Daily Living] explode all trees	13,194
25	“activities of daily living” OR acdl OR "funtional status":ti,ab,kw	15,369
26	MeSH descriptor: [Quality-Adjusted Life Years] explode all trees	2346
27	(“quality adjusted life years” OR "disability adjusted life years" OR qaly? OR daly? OR qald OR qale OR qtime OR qualy):ti,ab,kw	7089
28	MeSH descriptor: [Health Status] explode all trees	52,338
29	MeSH descriptor: [Sickness Impact Profile] explode all trees	637
30	(“standard gamble” OR "time trade off" OR "utility index" OR "visual analog"):ti,ab,kw	744,67
31	(“health utilit” OR disutilit* OR "utility value"):ti,ab,kw	339
32	(health status):ti	1489
33	“Carer Wellbeing and Support question” OR “Carer Well-being and Support question” OR “Impact of Alzheimer Disease on the Caregiver questionnaire” OR IADCQ OR “Caregiver Wellbeing Scale” OR “Caregiver Well-being Scale*” OR “Caregiver-targeted quality-of-life measure*” OR CGQOL OR CQOL OR “Caregiver Quality of Life Scale*” OR “caring questionnaire*” OR “Caregiver Quality of Life questionnaire*” OR “ASCOT-Carer*”	66

34	#6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33	308,759
35	#5 AND #34	5,670
36	(DEMQOL OR AD-5D OR “Alzheimer Disease Five Dimension” OR ("dementia-specific" NEAR/2 "quality of life")):ti,ab,kw	129
37	#35 OR #36	5,697
38	MeSH descriptor: [Caregivers] explode all trees	3,822
39	(carer* or caregiver*):ti	5,783
40	#38 OR #39	7,498
41	(EuroQol or euro NEXT qol or eq5d or "eq 5d" or 15d or 15 NEXT d or 15 NEXT dimension or AQoL or ((sf or shortform or short-form) NEAR (6d or "6 d" or 6 NEXT dimension)) or ((health NEXT utilit*) AND ind*) or hui2 or hui NEXT 2 or hui3 or hui NEXT 3 or "quality of wellbeing" or "quality of well-being" or QWB or sf36 or ((sf or shortform or short-form) NEAR ("36" or thirtysix or thirty NEXT six)) or CarerQoL or "ICECAP-O"):ti,ab,kw	33,468
42	#40 AND #41	306
43	#5 AND #42	102
44	#43 OR #37	5,700
45	#43 OR #37 with Cochrane Library publication date from Jan 1990 to Jun 2021	3,590
46	#43 OR #37 with Cochrane Library publication date from Jun 2021 to Aug 2023	1,029
47	#43 OR #37 with Cochrane Library publication date from Sep 2023 to May 2024	310
48	#45 OR #46 OR #47	4,929
49	“zarit” OR “zarit burden interview” OR “zarit caregiver burden interview”	731
50	#5 AND #49 with Cochrane Library publication date from Jan 1990 to May 2024	372
51	#48 OR #50	4,945

Table 96 Search strategy for PubMed (MEDLINE in process)

No.	Query	Results
#1	“dementia” OR “alzheimer disease”	266,412
#2	“Cognitive Dysfunction”	57,002
#3	(dementia* OR alzheimer*)	335,507
#4	((mild* OR early* OR preclinical OR pre-clinical) AND (“cognitive impair*” OR “cognitive dysfunction” OR “cognitive decline”))[Title]	51,947
#5	#1 OR #2 OR #3 OR #4	376,905
#6	”Quality of Life”	466,969
#7	(“quality of life” OR “quality of wellbeing” OR “quality of well-being”)[Title]	467,031

#8	(qol OR hqol OR HRQOL OR hrql OR hr-qol OR hr-ql OR euroqol OR “euro qol” OR eq5d OR eq-5d OR eq-vas OR vas OR whoqol OR “who qol” OR reqol*)[Title/Abstract]	651,018
#9	(sf6 OR sf6d OR sf12 OR sf16 OR sf20 OR sf36)[Title/Abstract]	35,268
#10	((sf OR shortform OR short-form) AND (“6” OR 6d OR “12” OR “16” OR “20” OR “36” OR six OR twelve OR sixteen OR twenty OR thirtysix OR “thirty six”))[Title/Abstract]	83,325
#11	(icepop OR icecap* OR “duke health profile” OR dhp OR “core outcome measure” OR “core outcome measures” OR “core om”)[Title/Abstract]	4,364
#12	(aaiqol OR aai-qol OR cdqlp OR qolas OR qolad OR qol-ad OR qold OR dqol OR demqol OR adrql OR adrqol OR oqold OR oqolda OR seiqol OR rsoc-qol OR qualid OR qualidem OR qwb-sa OR hsq-12 OR zbi OR zarit OR ces-d OR “activity and affect indicator*” OR dcm OR pwbcip OR pwb-cip OR npi-d OR ham-d OR basquid OR basqid OR stai OR stai-5 OR bdi OR gds OR gps OR hui OR hui-ii OR hui-iii OR isd OR pds OR pes-ad OR pesad OR pes-ad-aes OR pesadaes OR ghq OR cas OR cbs OR qwb OR cbi OR bsi OR srb OR phq-9)[Title/Abstract]	438,949
#13	(“modified coop*” OR “modified wonca*” OR “psychological well-being in cognitively impaired persons”)[Title/Abstract]	2,950
#14	“Personal Satisfaction” OR “Patient Satisfaction”	142,673
#15	((life OR patient* OR carer* OR caregiver* OR spous* OR wife OR wives OR husband) AND satisfaction) [Title]	207,329
#16	((life OR patient* OR carer* OR caregiver* OR spous* OR wife OR wives OR husband) AND (experience* OR preference* OR perspective*))[Title]	1,073,796
#17	"wellbeing"[Title] OR "well-being"[Title]	29,016
#18	“caregiver time”[Title/Abstract]	200
#19	#14 OR #15 OR #16 OR #17 OR #18	1,254,520
#20	“self report”	104,712
#21	(questionnaire* OR survey*)[Title/Abstract]	1,670,406
#22	(self report)[Title/Abstract]	72,030
#23	((patient* OR carer* OR caregiver* OR spous* OR wife OR wives OR husband? OR proxy) AND report*)[Title/Abstract]	2,579,097
#24	#20 OR #21 OR #22 OR #23	4,065,136
#25	#19 AND #24 AND #5	7,975
#26	“Caregiver*”	116,071
#27	((carer* OR caregiver* OR care OR spous* OR wife OR wives OR husband) AND (burden* OR cost?))[Title]	454,440
#28	“burden interview*”[Title]	82
#29	“value of life”[Title]	96
#30	”Activities of Daily Living”	90,755
#31	(“activities of daily living” OR acdl OR “funtional status”)[Title]	90,781
#32	“quality-adjusted life years”	22,309
#33	(“quality adjusted life years” OR “disability adjusted life years” OR qaly OR daly OR qald OR qale OR qtime OR qualy)[Title]	44,401

#34	“Health Status”	185,325
#35	“sickness impact profile”	8,098
#36	(“standard gamble” OR “time trade off” OR “utility index” OR “visual analog*”)[Title/Abstract]	89,050
#37	(health utilit* OR disutilit* OR “utility value*”)[Title/Abstract]	89,300
#38	“health status”[Title]	12,818
#39	((“Carer Wellbeing and Support question*”) OR (“Carer Well-being and Support question*”) OR “Impact of Alzheimer’s Disease on the Caregiver questionnaire*” OR IADCQ OR “Caregiver Wellbeing Scale*” OR “Caregiver Well-being Scale*” OR “Caregiver-targeted quality-of-life measure*” OR CGQOL OR CQOL OR “Caregiver Quality of Life Scale*” OR “caring questionnaire*” OR “Caregiver Quality of Life questionnaire*” OR “ASCOT-Carer*”)[Title/Abstract]	27,073
#40	#6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39	1,860,019
#41	#5 AND #40	52,233
#42	(DEMQOL* OR AD-5D OR “Alzheimer* Disease Five Dimension*” OR (“dementia-specific” AND “quality of life”))[Title/Abstract]	439
#43	#41 OR #42	52,424
#44	Caregivers* OR (carer* OR caregiver*)[Title]	131,457
#45	(EuroQol OR “euro qol” OR eq5d OR eq-5d OR 15d OR “15 d” OR “15 dimension” OR AQoL OR ((sf OR shortform OR short-form) AND (6d OR 6-d OR “6 dimension”)) OR “health utilit* ind*” OR hui2 OR “hui 2” OR hui3 OR “hui 3” OR “quality of wellbeing” OR “quality of well-being” OR QWB OR sf36 OR ((sf OR shortform OR short-form) AND (“36” OR thirtysix OR “thirty six”)) OR CarerQoL OR ICECAP-O)[Title/Abstract]	65,180
#46	#44 AND #45 AND #5	265
#47	#43 OR #46 OR #25	55,602
#48	“case reports” OR “phase I clinical trial” OR comment OR editorial OR letter OR “case study”	4,723,762
#49	“grounded theory” OR “qualitative research” OR (“qualitative research” OR “qualitative study” OR “qualitative interview*” OR “grounded theory” OR “hermeneutic*”)[Title/Abstract]	162,114
#50	#48 OR #49	4,878,015
#51	#47 NOT #50	49,504
#52	#47 NOT #50 Filters: English	46,487
#53	#47 NOT #50 Filters: English, from 1990/1/1 – 2017/4/1 – SLR 1	4,087
#54	#47 NOT #50 Filters: English, from 2017/4/1 – 2018/12/6 – SLR 2	1,044
#55	#47 NOT #50 Filters: English, from 2018/12/6 – 2020/3/1 – SLR 3	720
#56	#47 NOT #50 Filters: English, from 2020/3/1 – 2021/6/27 – SLR 4	1,085
#57	(#52 AND (inprocess[sb] OR pubstatusaheadofprint)) – SLR 5	530
#58	(#52 AND (inprocess[sb] OR pubstatusaheadofprint)) – SLR 6 (Current)	666
#59	#53 OR #54 OR #55 OR #56 OR #57 OR #58	8132

#60	“zarit” OR “zarit burden interview” OR “zarit caregiver burden interview”	1,732
#61	#5 AND #59	707
#62	(#60 AND (inprocess[sb] OR pubstatusaheadofprint)) – SLR 5	9
#63	(#60 AND (inprocess[sb] OR pubstatusaheadofprint)) – SLR 6 (current)	13
#64	#58 OR #61	8,135

Table 97 Search strategy for PsycInfo

No.	Query	Results
1	('Dementia' or 'AIDS Dementia Complex' or 'Dementia with Lewy Bodies' or 'Presenile Dementia' or 'Pseudodementia' or 'Semantic Dementia' or 'Senile Dementia' or 'Alzheimer Disease').mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures, mesh word]	108,917
2	'cognitive impairment'.mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures, mesh word]	66,535
3	dementia.m_titl. or alzheimer*.mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures, mesh word]	101,165
4	((mild* adj2 'cognitive impairment') or (mild* adj2 'cognitive impairments') or (early* adj2 'cognitive impairment') or (early* adj2 'cognitive impairments') or (preclinical adj2 'cognitive impairment') or (preclinical adj2 'cognitive impairments') or ('pre-clinical' adj2 'cognitive impairment') or ('pre-clinical' adj2 'cognitive impairments') or (mild* adj2 'cognitive dysfunction') or (early* adj2 'cognitive dysfunction') or (preclinical adj2 'cognitive dysfunction') or ('pre-clinical' adj2 'cognitive dysfunction') or (mild* adj2 'cognitive decline') or (early* adj2 'cognitive decline') or (preclinical adj2 'cognitive decline') or ('pre-clinical' adj2 'cognitive decline')).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures, mesh word]	16,425
5	#1 OR #2 OR #3 OR #4	2,174,097
6	('Quality of Life' or 'Health Related Quality of Life' or 'Quality of Work Life').mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures, mesh word]	113,207
7	('quality of life' or 'quality of wellbeing' or 'quality of well being').m_titl.	27,406
8	(qol or hqol or HRQOL or hrql or hr-qol or hr-ql or euroqol or ‘euro qol’ or eq5d or eq-5d or eq-vas or vas or whoqol or ‘who qol’ or reqol* or qol or hqol or HRQOL or hrql or hr-qol or hr-ql or euroqol or euro qol or eq5d or eq-5d or eq-vas or vas or whoqol or ‘who qol’ or reqol*).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures, mesh word]	28,895
9	(sf6 or sf6d or sf12 or sf16 or sf20 or sf36 or sf6 or sf6d or sf12 or sf16 or sf20 or sf36).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures, mesh word]	443
10	((sf adj1 ('Quality of Life' or 'Health Related Quality of Life' or 'Quality of Work Life')) or (sf adj1 6d) or (sf adj1 "12") or (sf adj1 "16") or (sf adj1 "20") or (sf adj1 "36") or (sf adj1 six) or (sf adj1 twelve) or (sf adj1 sixteen) or (sf adj1 twenty) or (sf adj1 thirtysix) or (sf adj1 'thirty six') or (shortform adj1 ('Quality of Life' or 'Health Related Quality of Life' or	14,404

	'Quality of Work Life')) or (shortform adj1 6d) or (shortform adj1 "12") or (shortform adj1 "16") or (shortform adj1 "20") or (shortform adj1 "36") or (shortform adj1 six) or (shortform adj1 twelve) or (shortform adj1 sixteen) or (shortform adj1 twenty) or (shortform adj1 thirtysix) or (shortform adj1 'thirty six') or ('short form' adj1 ('Quality of Life' or 'Health Related Quality of Life' or 'Quality of Work Life')) or ('short form' adj1 6d) or ('short form' adj1 "12") or ('short form' adj1 "16") or ('short form' adj1 "20") or ('short form' adj1 "36") or ('short form' adj1 six) or ('short form' adj1 twelve) or ('short form' adj1 sixteen) or ('short form' adj1 twenty) or ('short form' adj1 thirtysix) or ('short form' adj1 'thirty six') or (sf adj1 ('Quality of Life' or 'Health Related Quality of Life' or 'Quality of Work Life')) or (sf adj1 6d) or (sf adj1 "12") or (sf adj1 "16") or (sf adj1 "20") or (sf adj1 "36") or (sf adj1 six) or (sf adj1 twelve) or (sf adj1 sixteen) or (sf adj1 twenty) or (sf adj1 thirtysix) or (sf adj1 'thirty six') or (shortform adj1 ('Quality of Life' or 'Health Related Quality of Life' or 'Quality of Work Life')) or (shortform adj1 6d) or (shortform adj1 "12") or (shortform adj1 "16") or (shortform adj1 "20") or (shortform adj1 "36") or (shortform adj1 six) or (shortform adj1 twelve) or (shortform adj1 sixteen) or (shortform adj1 twenty) or (shortform adj1 thirtysix) or (shortform adj1 'thirty six') or ('short form' adj1 ('Quality of Life' or 'Health Related Quality of Life' or 'Quality of Work Life')) or ('short form' adj1 6d) or ('short form' adj1 "12") or ('short form' adj1 "16") or ('short form' adj1 "20") or ('short form' adj1 "36") or ('short form' adj1 six) or ('short form' adj1 twelve) or ('short form' adj1 sixteen) or ('short form' adj1 twenty) or ('short form' adj1 thirtysix) or ('short form' adj1 'thirty six')).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures, mesh word]	
11	(icepop or icecap* or 'duke health profile' or dhp or 'core outcome measure*' or 'core om' or icepop or icecap* or 'duke health profile' or dhp or 'core outcome measure*' or 'core om').mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures, mesh word]	694
12	(aaiqol or aai-qol or cdqlp or qolas or qolad or qol-ad or qold or dqol or demqol or adrql or adrqol or oqold or oqolda or seiqol or rsoc-qol or qualid or qualidem or qwb-sa or hsq-12 or zbi or zarit or ces-d or dcm or pwbcip or pwb-cip or npi-d or ham-d or basquid or basqid or stai or stai-5 or bdi or gds or gps or hui or hui-ii or hui-iii or isd or pds or pes-ad or pesad or pes-ad-aes or pesadaes or ghq or cas or cbs or qwb or cbi or bsi or srb or phq-9 or 'zarit burden interview' OR 'zarit caregiver burden interview').mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures, mesh word]	46,928
13	((modified adj1 coop*) or (modified adj1 wonca*) or 'psychological well-being in cognitively impaired persons').mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures, mesh word]	31
14	('Client Satisfaction' or 'Life Satisfaction').mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures, mesh word]	31,068
15	((life or patient* or carer* or caregiver* or spous* or wife or wives or husband) adj1 satisfaction).m_titl.	6,786
16	((life or patient* or carer* or caregiver* or spous* or wife or wives or husband) adj1 (experience* or preference* or perspective*)).m_titl.	5,424
17	(wellbeing or well-being).m_titl.	33,543

18	(‘caregiver time’ or ‘caregiver time’).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures, mesh word]	72
19	#14 OR #15 OR #16 OR #17 OR #18	63,584
20	(Questionnaires or Surveys or Self-Report).m_titl.	10,535
21	(questionnaire* or survey*).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures, mesh word]	893,688
22	'self report'.mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures, mesh word]	109,267
23	((patient* or carer* or caregiver* or spous* or wife or wives or husband* or proxy) adj1 report*).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures, mesh word]	23,089
24	#20 OR #21 OR #22 OR #23	972,762
25	#19 AND #24	31,020
26	'Caregiver Burden'.mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures, mesh word]	9,310
27	((carer* or caregiver* or care or spous* or wife or wives or husband*) adj2 (burden* or cost*)).m_titl.	1,986
28	"'burden interview*'".m_titl.	66
29	'value of life'.m_titl.	44
30	'Activities of Daily Living'.m_titl.	1,124
31	('activities of daily living' or acdl or 'funtional status').m_titl.	1,124
32	('quality adjusted life years' or 'disability adjusted life years' or qaly* or daly* or qald or qale or qtime or qualy).m_titl.	207
33	('standard gamble' or 'time trade off' or 'utility index' or (visual adj1 analog*)).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures, mesh word]	24,001
34	((health adj1 utilit*) or disutilit* or (utility adj1 value*)).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures, mesh word]	2,033
35	'health status'.m_titl.	3,030
36	(('Carer Wellbeing' and (Support adj1 question*)) or ('Carer Well-being' and (Support adj1 question*)) or ('Impact of Alzheimer* Disease' and (Caregiver adj1 questionnaire*)) or IADCQ or ('Caregiver Wellbeing' adj1 Scale*) or ('Caregiver Well-being' adj1 Scale*) or ('Caregiver-targeted quality-of-life' adj1 measure*) or CGQOL or CQOL or ('Caregiver Quality of Life' adj1 Scale*) or (caring adj1 questionnaire*) or ('Caregiver Quality of Life' adj1 questionnaire*) or (ASCOT adj1 Carer*)).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures, mesh word]	146
37	#6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36	1,411,237
38	#5 AND #37	15,676
39	(DEMQOL* or AD-5D or (Alzheimer* and ('Disease Five' adj1 Dimension*)) or (dementia-specific adj4 'quality of life')).mp. [mp=title,	97

	abstract, heading word, table of contents, key concepts, original title, tests & measures, mesh word]	
40	#38 OR #39	64,085
41	('Caregiver Burden' or carer* or caregiver*).m_titl.	21,891
42	(EuroQol or 'euro qol' or eq5d or eq-5d or 15d or '15 d' or '15 dimension' or AQoL or ((sf or shortform or short-form) adj1 (6d or 6-d or '6 dimension')) or ((health adj1 utilit*) and ind*) or hui2 or hui 2 or hui3 or hui 3 or 'quality of wellbeing' or 'quality of well-being' or QWB or sf36 or ((sf or shortform or short-form) adj1 (('Carer Wellbeing' and (Support adj1 question*)) or ('Carer Well-being' and (Support adj1 question*)) or ('Impact of Alzheimer* Disease' and (Caregiver adj1 questionnaire*)) or IADCQ or ('Caregiver Wellbeing' adj1 Scale*) or ('Caregiver Well-being' adj1 Scale*) or ('Caregiver-targeted quality-of-life' adj1 measure*) or CGQOL or CQOL or ('Caregiver Quality of Life' adj1 Scale*) or (caring adj1 questionnaire*) or ('Caregiver Quality of Life' adj1 questionnaire*) or (ASCOT adj1 Carer*) or thirtysix or thirty six)) or CarerQoL or ICECAP-O).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures, mesh word]	6,784
43	#41 AND #42	3,010
44	#40 OR #43	73,262
45	('Case Report' or 'case study' or letter* or editorial).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures, mesh word]	212,050
46	('Grounded Theory' or 'Qualitative Methods' or 'qualitative research' or 'qualitative study' or (qualitative adj1 interview*) or 'grounded theory' or hermeneutic*).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures, mesh word]	134,464
47	#45 OR #46	327,721
48	#44 NOT #47	14,295
49	limit 48 to yr="1990 - 2023"	9,299
50	limit 48 to yr="2021 - 2023"	1,670
51	limit 48 to yr="2023 - 2024"	1,615

Table 98 Search strategy for Embase (Embase + MEDLINE) supplementary search for caregiver burden

No.	Query	Results
1	'alzheimer disease'/mj/exp OR 'alzheimer disease' OR alzheimer*:ti OR 'mild cognitive impairment'/exp OR 'mild cognitive impairment'	149,921
2	((mild* NEAR/2 'cognitive impairment'):ti) OR ((mild* NEAR/2 'cognitive impairments'):ti) OR ((early* NEAR/2 'cognitive impairment'):ti) OR ((early* NEAR/2 'cognitive impairments'):ti) OR ((preclinical NEAR/2 'cognitive impairment'):ti) OR ((preclinical NEAR/2 'cognitive impairments'):ti) OR (('pre-clinical' NEAR/2 'cognitive impairment'):ti) OR (('pre-clinical' NEAR/2 'cognitive impairments'):ti) OR ((mild* NEAR/2 'cognitive dysfunction'):ti) OR ((early* NEAR/2 'cognitive dysfunction'):ti) OR ((preclinical NEAR/2 'cognitive dysfunction'):ti) OR (('pre-clinical' NEAR/2 'cognitive dysfunction'):ti) OR ((mild* NEAR/2 'cognitive decline'):ti) OR ((early* NEAR/2 'cognitive decline'):ti) OR ((preclinical	12,810

	NEAR/2 'cognitive decline'):ti) OR (('pre-clinical' NEAR/2 'cognitive decline'):ti)	
3	#1 OR #2	151,821
4	'quality of life'/exp/mj	117,607
5	'quality of life':ti OR 'quality of wellbeing':ti OR 'quality of well-being':ti	112,804
6	qol:ti,ab OR hqol:ti,ab OR hrqol:ti,ab OR hrql:ti,ab OR 'hr-qol':ti,ab OR 'hr-ql':ti,ab OR euroqol:ti,ab OR 'euro qol':ti,ab OR eq5d:ti,ab OR 'eq-5d':ti,ab OR 'eq-vas':ti,ab OR vas:ti,ab OR whoqol:ti,ab OR 'who qol':ti,ab OR reqol*:ti,ab	206,164
7	sf6:ti,ab OR sf6d:ti,ab OR sf12:ti,ab OR sf16:ti,ab OR sf20:ti,ab OR sf36:ti,ab	5,744
8	((sf NEAR/1 6):ti,ab) OR ((sf NEAR/1 6d):ti,ab) OR ((sf NEAR/1 12):ti,ab) OR ((sf NEAR/1 16):ti,ab) OR ((sf NEAR/1 20):ti,ab) OR ((sf NEAR/1 36):ti,ab) OR ((sf NEAR/1 six):ti,ab) OR ((sf NEAR/1 twelve):ti,ab) OR ((sf NEAR/1 sixteen):ti,ab) OR ((sf NEAR/1 twenty):ti,ab) OR ((sf NEAR/1 thirtysix):ti,ab) OR ((sf NEAR/1 'thirty six'):ti,ab) OR ((shortform NEAR/1 6):ti,ab) OR ((shortform NEAR/1 6d):ti,ab) OR ((shortform NEAR/1 12):ti,ab) OR ((shortform NEAR/1 16):ti,ab) OR ((shortform NEAR/1 20):ti,ab) OR ((shortform NEAR/1 36):ti,ab) OR ((shortform NEAR/1 six):ti,ab) OR ((shortform NEAR/1 twelve):ti,ab) OR ((shortform NEAR/1 sixteen):ti,ab) OR ((shortform NEAR/1 twenty):ti,ab) OR ((shortform NEAR/1 thirtysix):ti,ab) OR ((shortform NEAR/1 'thirty six'):ti,ab) OR (('short form' NEAR/1 6):ti,ab) OR (('short form' NEAR/1 6d):ti,ab) OR (('short form' NEAR/1 12):ti,ab) OR (('short form' NEAR/1 16):ti,ab) OR (('short form' NEAR/1 20):ti,ab) OR (('short form' NEAR/1 36):ti,ab) OR (('short form' NEAR/1 six):ti,ab) OR (('short form' NEAR/1 twelve):ti,ab) OR (('short form' NEAR/1 sixteen):ti,ab) OR (('short form' NEAR/1 twenty):ti,ab) OR (('short form' NEAR/1 thirtysix):ti,ab) OR (('short form' NEAR/1 'thirty six'):ti,ab)	52,857
9	icepop:ti,ab OR icecap*:ti,ab OR 'duke health profile':ti,ab OR dhp:ti,ab OR ((core NEXT/1 outcome NEXT/1 measure*):ti,ab) OR 'core om':ti,ab	4,448
10	aaiqol:ti,ab OR 'aai-qol':ti,ab OR cdqlp:ti,ab OR qolas:ti,ab OR qolad:ti,ab OR 'qol-ad':ti,ab OR qold:ti,ab OR dqol:ti,ab OR demqol:ti,ab OR adrql:ti,ab OR adrqol:ti,ab OR oqold:ti,ab OR oqolda:ti,ab OR seiqol:ti,ab OR 'rsoc-qol':ti,ab OR qualid:ti,ab OR qualidem:ti,ab OR 'qwb-sa':ti,ab OR 'hsq-12':ti,ab OR zbi:ti,ab OR zarit:ti,ab OR 'ces-d':ti,ab OR 'activity and affect indicator*':ti,ab OR dcm:ti,ab OR pwbcip:ti,ab OR 'pwb-cip':ti,ab OR 'npi-d':ti,ab OR 'ham-d':ti,ab OR basquid:ti,ab OR basqid:ti,ab OR stai:ti,ab OR 'stai-5':ti,ab OR bdi:ti,ab OR gds:ti,ab OR gps:ti,ab OR hui:ti,ab OR 'hui-ii':ti,ab OR 'hui-iii':ti,ab OR isd:ti,ab OR pds:ti,ab OR 'pes-ad':ti,ab OR pesad:ti,ab OR 'pes-ad-aes':ti,ab OR pesadaes:ti,ab OR ghq:ti,ab OR cas:ti,ab OR cbs:ti,ab OR qwb:ti,ab OR cbi:ti,ab OR bsi:ti,ab OR srb:ti,ab OR 'phq-9':ti,ab	172,244
11	((modified NEXT/1 coop*):ti,ab) OR ((modified NEXT/1 wonca*):ti,ab) OR 'psychological well-being in cognitively impaired persons':ti,ab	39
12	'daily life activity'/mj	14,733
13	'activities of daily living':ti OR acdl:ti OR 'funtional status':ti	3,338
14	'quality adjusted life year'/mj	1,775
15	'quality adjusted life years':ti OR 'disability adjusted life years':ti OR qaly?:ti OR daly?:ti OR qald:ti OR qale:ti OR qtime:ti OR qualy:ti	908
16	'health status'/mj	36,200

17	'sickness impact profile'/mj	719
18	'standard gamble':ti,ab OR 'time trade off':ti,ab OR 'utility index':ti,ab OR ((visual NEXT/1 analog*):ti,ab)	98,668
19	((health NEXT/1 utilit*):ti,ab) OR disutilit*:ti,ab OR ((utility NEXT/1 value?):ti,ab)	6,922
20	demqol*:ti,ab OR 'ad 5d':ti,ab OR (alzheimer*:ti,ab AND disease:ti,ab AND five:ti,ab AND dimension*:ti,ab) OR ('dementia specific':ti,ab AND quality:ti,ab AND of:ti,ab AND life:ti,ab)	420
21	euroqol:ti,ab OR 'euro qol':ti,ab OR eq5d:ti,ab OR 'eq-5d':ti,ab OR 15d:ti,ab OR '15 d':ti,ab OR '15 dimension':ti,ab OR aqol:ti,ab OR (((sf OR shortform OR 'short-form') NEAR/1 (6d OR '6-d' OR '6 dimension')):ti,ab) OR 'health utilit* ind*':ti,ab OR hui2:ti,ab OR 'hui 2':ti,ab OR hui3:ti,ab OR 'hui 3':ti,ab OR 'quality of wellbeing':ti,ab OR 'quality of well-being':ti,ab OR qwb:ti,ab OR sf36:ti,ab OR (((sf OR shortform OR 'short-form') NEAR/1 ('36' OR thirtysix OR 'thirty six')):ti,ab) OR carerqol:ti,ab OR 'icecap-o':ti,ab	73,444
22	#4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21	558,836
23	((carer? OR caregiver? OR spous* OR wife OR wives OR husband?) NEAR/1 satisfaction):ti	40
24	((carer? OR caregiver? OR spous* OR wife OR wives OR husband?) NEAR/1 (experience? OR preference? OR perspective?)):ti	537
25	'caregiver time':ti,ab	266
26	((carer? OR caregiver? OR spous* OR wife OR wives OR husband?) NEAR/1 report?):ti,ab	310
27	'caregiver burden'/mj	3,545
28	((carer? OR caregiver? OR care OR spous* OR wife OR wives OR husband?) NEAR/2 burden*):ti	1,165
29	'caregiver'/mj OR carer?:ti OR caregiver?:ti	33,912
30	#23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29	36,672
31	#3 AND #22 AND #30	499
32	'carer wellbeing and support question*':ti,ab OR 'carer well-being and support question*':ti,ab OR 'impact of alzheimers disease on the caregiver questionnaire*':ti,ab OR iadcq:ti,ab OR 'caregiver wellbeing scale*':ti,ab OR 'caregiver well-being scale*':ti,ab OR 'caregiver-targeted quality-of-life measure*':ti,ab OR cgqol:ti,ab OR cqol:ti,ab OR 'caregiver quality of life scale*':ti,ab OR 'caring questionnaire*':ti,ab OR 'caregiver quality of life questionnaire*':ti,ab OR 'ascot-carer*':ti,ab	148
33	#31 OR #32	643
34	'phase 1 clinical trial'/de OR 'case report'/de OR 'case report':ti OR 'case study':ti	2,839,248
35	'grounded theory'/de OR 'qualitative research'/exp OR 'qualitative research':ti,ab OR 'qualitative study':ti,ab OR ((qualitative NEXT/1 interview*):ti,ab) OR 'grounded theory':ti,ab OR hermeneutic*:ti,ab	131,500
36	#34 OR #35	2,967,976
37	#33 NOT #36	612

38	#33 NOT #36 AND ([conference review]/lim OR [editorial]/lim OR [letter]/lim OR [note]/lim OR [review]/lim OR [short survey]/lim)	23
39	#33 NOT #36 AND [animals]/lim	4
40	#38 OR #39	27
41	#37 NOT #40	585
42	#37 NOT #40 AND [english]/lim	551
43	#37 NOT #40 AND [english]/lim AND [1990-2017]/py	420

I.1.3 Systematic selection of the studies

Initial screening of the retrieved citations was undertaken based on the title and abstract. Citations that did not match the eligibility criteria were excluded at this 'first pass' stage. If there was lack of clarity on whether citations were eligible for the review due to limited information in the abstract, these citations were included for 'second pass' stage. Two independent reviewers screened all citations and full text papers and any discrepancies in their decisions were resolved by a third reviewer. Citation duplicates (due to the overlap in the coverage of the databases) were also excluded at this stage. Upon acceptance during the initial screening, full-text copies of all references that could potentially meet the eligibility criteria were retrieved.

The full-text publications of all citations of potential interest were then screened for inclusion. Two independent reviewers screened all citations and full text papers and any discrepancies in their decisions were resolved by a third reviewer. Citations that did not match the eligibility criteria were excluded at this 'second-pass' stage. At the full text screening stage, if there was lack of clarity on whether the publication met the eligibility criteria, these citations were excluded. Full-text screening was followed by linking of multiple publications. Studies meeting the eligibility criteria at the second screening stage were extracted.

The inclusion and exclusion criteria was further refined for Danish adaption.

Table 99 Inclusion and exclusion criteria used for assessment of studies

Clinical effectiveness	Inclusion criteria	Exclusion criteria	Changes, local adaption
Population	Disease: Patients with MCI (irrespective of causality) and/or AD (irrespective of severity) Age: Adult (≥18 years) patients Race: No restriction Gender: No restriction	Disease: Patients with a specific type of dementia other than AD, e.g., Parkinson's, vascular dementia, or frontotemporal dementia Age: Studies evaluating children Race: N/A Gender: N/A	N/A

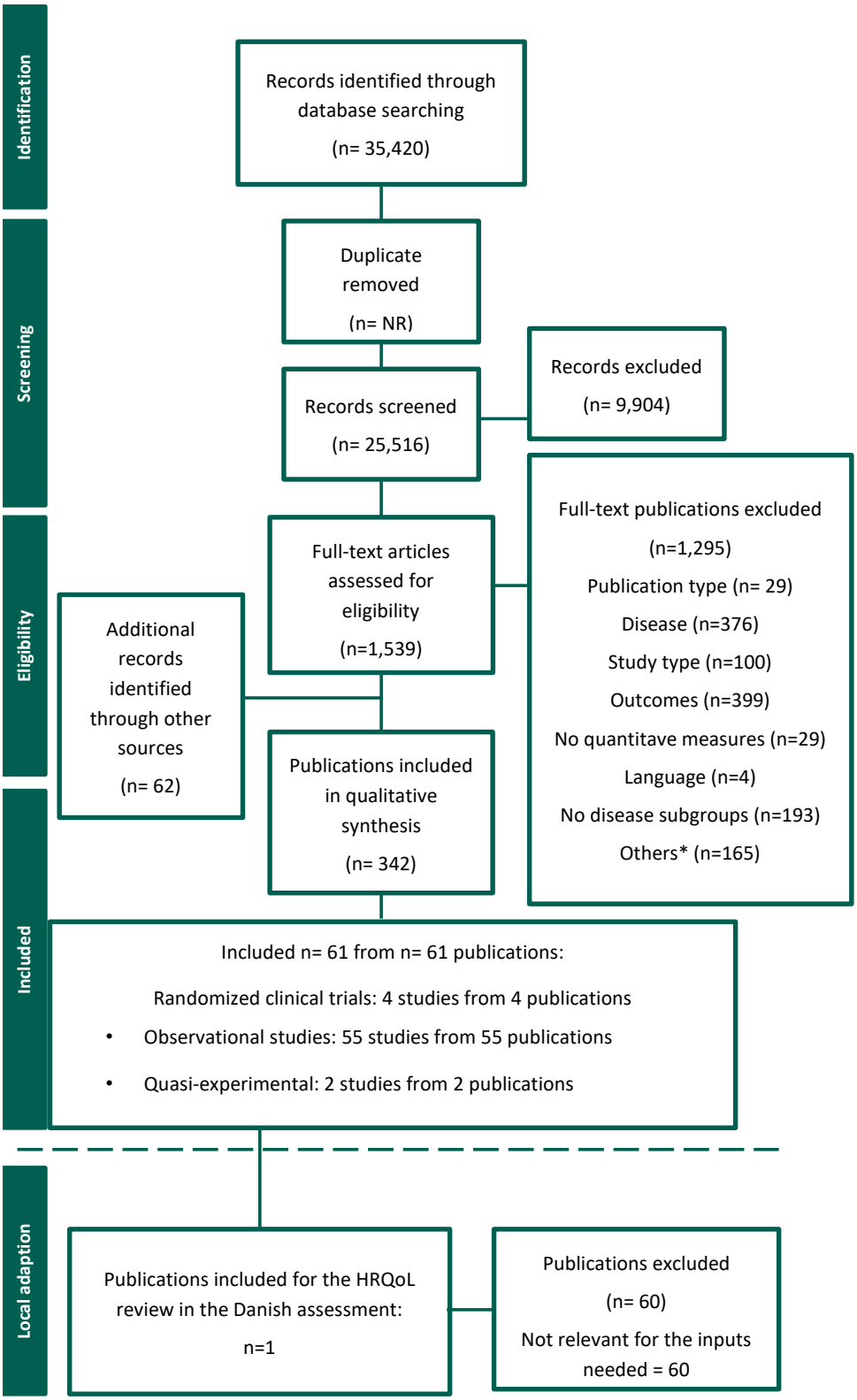
Intervention	No restrictions	N/A	N/A
Comparators	No restrictions	N/A	N/A
Outcomes	Information on recruitment, response rates, description of health states, adverse reactions, appropriateness of health states, care setting, methods of elicitation/valuation, mapping, and uncertainty around values	Studies not reporting relevant outcomes of interest were excluded	The study to be leverage in the economic model was selected based on several factors as alignment with model structure and inputs need.
Study design/publication type	Study design: No restriction, all the interventional and observational studies will be considered for inclusion. Publication type: Peer-reviewed journal articles and conference abstracts Editorials, newspaper articles, book sections, letter, expert opinion or commentary, trial protocols, and reviews	Study design: N/A Publication type: Editorials, newspaper articles, book sections, letter, expert opinion or commentary, trial protocols, and reviews	N/A
Language restrictions	English language	Non-English	N/A
Time frame	January 1st, 1990, to May 1st, 2024	Studies published before 1990	N/A
Others	N/A	Studies conducted in-vitro and animals • Studies using a qualitative data collection method only, i.e., no quantitative measure • Studies were excluded if they focused on the development and validation of HRQoL instruments	N/A

Abbreviations: AD, Alzheimer's disease; HRQoL, Health related quality of life; MCI, Mild cognitive impairment:; N/A = Not applicable

The literature search yielded 35,482 separate references (35,420 from databases and 62 from additional sources). Following the first pass of the publications, 1,637 potentially relevant publications were identified. Full-text reports of these publications were retrieved for a more detailed evaluation. In total, 60 studies were identified.

From the 47 publications included, one was leveraged in the economic analysis (Farina et al. 2020 (74)).

Figure 32 PRISMA flow chart



15.1.1 Excluded full text references

The reference included in Table 100, in addition to Farina et al. 2020 (74) were included in the global SLR. For the local adaptation, only Farina et al. 2020 (74) was leveraged in the economic analysis.

Table 100 Overview of excluded studies

Reference	Reason for exclusion
Dixit D. et al., Quality of Life Assessments in Individuals With Young-Onset Dementia and Their Caregivers J Geriatr Psychiatry Neurol. 2020(34)5:426-433	Not relevant
Handels R. et al., Quality of Life, Care Resource Use, and Costs of Dementia in 8 European Countries in a Cross-Sectional Cohort of the Actifcare Study Journal of Alzheimer's Disease. 2018(66):1027-1040	Not relevant
Black C. et al., Non-professional caregiver burden is associated with the severity of patients' cognitive impairment PLoS One . 2018(13): e0204110	Not relevant
Park M. et al., Change in Health-related Quality of Life After Referral to Memory Assessment Services Alzheimer Dis Assoc Disord . 2017(31):192-199	Not relevant
Fang M. et al., A comparison of health utility scores calculated using United Kingdom and Canadian preference weights in persons with alzheimer's disease and their caregivers Health & Quality of Life Outcomes. 2016(14)105.	Not relevant
Orgeta V. et al., The use of the EQ-5D as a measure of health-related quality of life in people with dementia and their carers. Qual Life Res. 2015(24) 2:315-324	Not relevant
Trigg R. et al., The relationship between changes in quality-of-life outcomes and progression of Alzheimer's disease: results from the dependence in AD in England 2 longitudinal study Int J Geriatr Psychiatry. 2015(30) 4:400-408	Not relevant
Jones R.W. et. Al., Dependence in Alzheimer's disease and service use costs, quality of life, and caregiver burden: The DADE study Alzheimer's and Dementia. 2015(11) 3:280-290	Not relevant
Bleijlevens M. et al., Changes in caregiver burden and health-related quality of life of informal caregivers of older people with Dementia: evidence from the European RightTimePlaceCare prospective cohort study J Adv Nurs . 2015(71):1378-1391	Not relevant
Mulhern B. et al., Development of DEMQOL-U and DEMQOL-PROXY-U: generation of preference-based indices from DEMQOL and DEMQOL-PROXY for use in economic evaluation. Health Technol Assess. 2013(17)5:1-160	Not relevant
Bradshaw L. et al., Carers for older people with co-morbid cognitive impairment in general hospital: characteristics and psychological well-being Int J Geriatr Psychiatry. 2013(28):681-690	Not relevant
Wimo A. et al., The GERAS Study: a prospective observational study of costs and resource use in community dwellers with Alzheimer's disease in	Not relevant

three European countries--study design and baseline findings J Alzheimer Dis. 2013(36)2:385-399	
Woods RT. et al., REMCARE: reminiscence groups for people with dementia and their family caregivers - effectiveness and cost-effectiveness pragmatic multicentre randomised trial. Health Technol Assess. 2012(16) 48:1-116	Not relevant
Sheehan BD. et al., Patient and proxy measurement of quality of life among general hospital in-patients with dementia. Aging Ment Health. 2012(16) 5:603-607	Not relevant
Selwood A. et al., Quality of life in dementia – a one-year follow-up study. Int J Geriatr Psychiatry. 2005(20) 3:232-237	Not relevant
Bryan S. et al., Proxy completion of EQ-5D in patients with dementia Qual Life Res.2005(14)1:107-118	Not relevant
Thorgrimse L. et al., Whose quality of life is it anyway? The validity and reliability of the Quality of Life-Alzheimer's Disease (QoL-AD) scale Alzheimer Dis Assoc Disord. 2003(17) 4:201-208	Not relevant
Coucill W. et al., EQ-5D in patients with dementia: an investigation of inter-rater agreement Med Care. 2001(39) 8:760-771	Not relevant
Moriya M. et al., Estimation of cognitive impairment in chronic pain patients and characteristics of estimated mild cognitive impairment Frontiers in Neurology. 2024(15)	Not relevant
Vermeulen R.J. et al., Prognostic Information on Progression to Dementia: Quantification of the Impact on Quality-of-Life Journal of Alzheimer's Disease. 2024(97) 4:1829-1840	Not relevant
Lanctôt K. et al., Cost consequence analysis of Apathy in Dementia Methylphenidate Trial 2 (ADMET 2) International psychogeriatrics. 2023(35) 11:664-672	Not relevant
Mank A et al., longitudinal study on quality of life along the spectrum of Alzheimer’s disease Alzheimer's Research and Therapy. 2022(132)	Not relevant
Tan K.P et al., Relationship of Psychological Flexibility and Mindfulness to Caregiver Burden, and Depressive and Anxiety Symptoms in Caregivers of People with Dementia International Journal of Environmental Research and Public Health. 2023 20:5 Article Number: 4232.	Not relevant
Eikelboom W.S. et al., Effects of the DICE Method to Improve Timely Recognition and Treatment of Neuropsychiatric Symptoms in Early Alzheimer's Disease at the Memory Clinic: The BEAT-IT Study Journal of Alzheimer's Disease. 2023(93) 4:1407-1423	Not relevant
Aye S. et al., Health-related quality of life in subjective cognitive decline and mild cognitive impairment: a longitudinal cohort analysis Alzheimer's Research and Therapy. 2023(15)	Not relevant
Stites S.D. et al., Awareness of diagnosis predicts changes in quality of life in individuals with mild cognitive impairment and mild stage dementia International Journal of Geriatric Psychiatry (2023) 38:6 Article Number: e5939. Date of Publication: 1 Jun 2023. 2023(38)6	Not relevant

Van Hezik- Wester V.J. et al., Caregiver Burden and Quality of Life Across Alzheimer's Disease Severity Stages Alzheimer Disease and Associated Disorders. 2023 37(2):134-141.	Not relevant
Saitoh Y. et al., Randomized, sham-controlled, clinical trial of repetitive transcranial magnetic stimulation for patients with Alzheimerâ€™s dementia in Japan Frontiers in Aging Neuroscience (2022) 14 Article Number: 993306.	Not relevant
Leiva N. et al., Frailty and quality of life in elderly (QoL) with cognitive impairment (CI) or Mild Cognitive Impairment (MCI) living in the community European Geriatric Medicine (2022) 13 Supplement 1 (S167).	Not relevant
Simons C. et al., Mapping Quality of Life - Alzheimer's Disease (QOL-AD) Scores to EQ-5D-5L Utilities in the Ambar Trial Population Value in Health (2022) 25:1 Supplement (S13).	Not relevant
Im E.O. et al., Attitudes toward Alzheimer's disease and dementia caregiving and health outcomes: Racial and ethnic differences Geriatric nursing (New York, N.Y.) (2022) 48 (296-302).	Not relevant
Mank A. et al., A longitudinal study on quality of life along the spectrum of Alzheimer's disease Alzheimer's Research and Therapy (2022) 14:1 Article Number: 132.	Not relevant
Gustavsson A. et al. Health utility in preclinical and prodromal Alzheimer's disease for establishing the value of new disease-modifying treatments—EQ-5D data from the Swedish BioFINDER study. Alzheimer's & Dementia 17.11 (2021): 1832-1842.	Not relevant
Ashizawa T. et al., Impact of the severity of alzheimer's disease on the quality of life, activities of daily living, and caregiving costs for institutionalized patients on anti-alzheimer medications in japan Journal of Alzheimer's Disease. 2021(81) 1:367-374	Not relevant
Junaid Farrukh M. et al., Medication adherence status among patients with neurological conditions and its association with quality of life. Saudi pharmaceutical journal. 2021(29) 5:427-433	Not relevant
Liu H-Y. et al., T Relationships between cognitive dysfunction and health-related quality of life among older persons in Taiwan: a nationwide population-based survey Am J Alzheimers Dis Other Dement. 2019(34) 1:41-48	Not relevant
Kongpakwattana K. et al., A real-world evidence analysis of associations among costs, quality of life, and disease-severity indicators of Alzheimer's disease in Thailand Value Health. 2019(22) 10:1137-1145	Not relevant
Bruno, G. et al., Costs and resource use associated with Alzheimer's disease in Italy: Results from an observational study Journal of Prevention of Alzheimer's Disease. 2018(5) 1:55-64	Not relevant
Montgomery W. et al., Alzheimer's disease severity and its association with patient and caregiver quality of life in Japan: results of a community-based survey BMC Geriatr. 2018(18) 1-12	Not relevant
Hvidsten L, et al., Quality of Life in People with Young-Onset Alzheimer's Dementia and Frontotemporal Dementia Dement Geriatr Cogn Disord. 2018(45):91-104	Not relevant

Majoni, M. et al., Does being a retired or employed caregiver affect the association between behaviours in Alzheimer's disease and caregivers' health-related quality-of-life? BMC Research Notes. 2017(10): 1-6	Not relevant
Olazaran j. et al., Costs and quality of life in community-dwelling patients with Alzheimer's disease in Spain: results from the GERAS II observational study International Psychogeriatrics. 2017(29): 2081-2093	Not relevant
Reed C. et al., Factors associated with long-term impact on informal caregivers during Alzheimer's disease dementia progression: 36-month results from GERAS Int Psychogeriatr. 2020(32) 2:267-277	Not relevant
Garre-Olmo J. et al., A path analysis of dependence and quality of life in Alzheimer's disease. Am J Alzheimers Dis Other Demen. 2017(32) 2:108-115	Not relevant
Fang M. et al., A comparison of health utility scores calculated using United Kingdom and Canadian preference weights in persons with alzheimer's disease and their caregivers Health and Quality of Life Outcomes. 2016(14): 1-8	Not relevant
Hoffmann K. et al., Moderate-to-high intensity physical exercise in patients with Alzheimer's disease: a randomized controlled trial J Alzheimers Dis. 2016(50)2: 443-453	Not relevant
Oremus M. et al. Can the general public use vignettes to discriminate between Alzheimer's disease health states? BMC geriatrics. 2016(16):1-7	Not relevant
Hessmann P. et al., Health-related quality of life in patients with Alzheimer's disease in different German health care settings. J Alzheimers Dis. 2016(51)2: 545-561	Not relevant
Oremus, M. et al., Health utility scores in Alzheimer's disease: differences based on calculation with American and Canadian preference weights Value Health. 2014(17): 77-83	Not relevant
Xie F. et al., Measuring health-related quality-of-life for Alzheimer's disease using the general public. Quality of life research: an international journal of quality-of-life aspects of treatment, care and rehabilitation. 2012(21) 4:593-601	Not relevant
Tarride J. et al., How does the Canadian general public rate moderate Alzheimer's disease? Journal of Aging Research. 2011(2011):682470	Not relevant
Naglie G. et al., Predictors of family caregiver ratings of patient quality of life in Alzheimer disease: cross-sectional results from the Canadian Alzheimer's Disease Quality of Life Study. American Journal of Geriatric Psychiatry. 2011(19) 10:891-901	Not relevant
McLaughlin T. et al., Assessment of potential measures in models of progression in Alzheimer disease. Neurology. 2010(75) 14:1256-1262	Not relevant
Mesterton J. et al., Cross Sectional Observational Study on the Societal Costs of Alzheimer's Disease Curr Alzheimer Res. 2010(7):358-367	Not relevant
Karlawish J.H. et al., Preference-based quality of life in patients with Alzheimer's disease Alzheimers Dement. 2008(4) 3:193-202	Not relevant
Karlawish J.H. et al., Caregivers' assessments of preference-based quality of life in Alzheimer's disease Alzheimers Dement. 2008(4) 3:203-211	Not relevant

Boström F. et al., Patients with dementia with lewy bodies have more impaired quality of life than patients with Alzheimer disease. Alzheimer Dis Assoc Disord.. 2007(21) 2:150-154	Not relevant
Lopez-Bastida J. et al., Social-economic costs and quality of life of Alzheimer disease in the Canary Islands, Spain. Neurology. 2006(67) 12:2186-2191	Not relevant
Naglie G. et al., Utility-based quality of life measures in Alzheimer's disease. Quality of Life Research. 2006(15) 4:631-643	Not relevant
Jonsson L. et al., Patient- and Proxy-Reported Utility in Alzheimer Disease Using the EuroQoL Alzheimer Dis Assoc Disord. 2006(20):49-55	Not relevant

Table 101 Results from the SLR leveraged in this assessment

Reference	Study design and patients' population	Recruitment	Instrument
Farina et al. 2020 (74)	Patients with dementia (mixed cause) and their carers	Patients were recruited from a cross-sectional data from a cohort study (MODEM study)	Self-report measures (person with dementia): DEMQOL, EQ-5D, CASP-19 Proxy-report measures (person with dementia): DEMQOL-Proxy, EQ-5D Self-report measures (carer): EQ-5D, SF-12 UK specific tariff applied for EQ-5D data

Abbreviations: CASP-19 = Control, Autonomy, Self-realisation, and Pleasure – 19 items; DEMQOL = Dementia Quality of Life; EQ-5D = EuroQol 5-Dimension; N/A = Not applicable; SF-12: 12-Item Short Form Health Survey

I.1.4 Quality assessment and generalizability of estimates

There are factors that might limit the generalisability of the estimates reported by Farina et al. (2020) (74), including heterogeneity in population preferences and the presence of confounding variables that influence quality of life across different stages of the disease—such as caregiver availability, healthcare system characteristics, and quality of assistance. Nevertheless, while variation in population preferences constitutes a recognized limitation, the influence of confounders affecting patient quality of life is particularly challenging to quantify, as their relative impact is not only highly context-dependent but also difficult to isolate both across countries and within national settings.

Specific estimates from the Danish settings were not considered relevant as not providing values in a format that could directly be leverage in the economic analysis or considered dated compared to Farina et al. 2020 (74).

I.1.5 Unpublished data

N/A

Appendix J. Literature searches for input to the health economic model

J.1 Literature search for TP

J.1.1.1 Objective

This review specifically aimed to identify model inputs concerning TP between health states for the economic model evaluating the use of lecanemab in AD

A global SLR was used to select the relevant information for the Danish adaptation.

J.1.1.2 Methods

This literature review is based on a reproducible and validated comprehensive search of the evidence. The SLRs were conducted according to the general recommendations of the Cochrane Handbook for Systematic Reviews of Interventions A full protocol for the literature review was developed prior to the review for detailing the patient population, interventions, and study designs to be included. The SLR was reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (149).

J.1.1.3 Information sources

J.1.1.3.1 Bibliographical databases

The databased used in the TP literature search are summarised in Table 91.

Table 102 Bibliographic databases included in the literature search

Database	Platform	Relevant period for the search	Date of search completion
Embase	Embase.com	Database inception to August 31, 2023	31.08.2023
Medline	www.ncbi.nlm.nih.gov/sites/entrez	Database inception to August 31, 2023	31.08.2023
Cochrane Library	mrw.interscience.wiley.com/cochrane/cochrane_search_fs.html	Database inception to August 31, 2023	31.08.2023

J.1.1.3.2 Conference proceedings

Supplementary searches of conference proceedings were reported for the previous five years (2020-24) as listed in Table 93. Since many conference proceedings are now included within Embase, one reviewer checked the coverage of specific conferences of interest by checking the Embase list of conferences (https://www.elsevier.com/solutions/embase-

biomedical-research/coverage-and-content). In addition, because of Cochrane's Embase project, conference abstracts that are indexed in Embase and are reports of RCTs are now being included in CENTRAL. As per the findings of Cochrane methodology reviews, trials with positive results tended to be published in approximately 4 to 5 years. Thereby, we restricted the manual handsearching of conference proceedings to the last four years.

Table 103 Conference material included in the literature search

Conference	Source of abstracts	Search strategy	Words/terms searched	Date of search
AAIC - Annual Alzheimer's Association International Conference.	Conference website (https://aaic.alz.org/abstracts/abstracts-archive.asp) and Embase	Hand search	N/A	01.05.2024
EAN – Annual Congress of the European Academy of Neurology	[redacted] and Embase	Hand search	N/A	01.05.2024
ANA – American Neurological Association	https://myana.org/	Hand search	N/A	01.05.2024
AAN – American Academy of Neurology	[redacted] and Embase	Hand search	N/A	01.05.2024
ADI - International Conference of Alzheimer's Disease International	https://adiconference.org/files/general/ADI-2022-Abstract-Book.pdf	Hand search	N/A	01.05.2024
CTAD- Clinical Trials on Alzheimer's Disease	https://www.ctad-alzheimer.com/ and Embase	Hand search	N/A	01.05.2024
ISPOR – International Society for Pharmacoeconomics and Outcomes Research	[redacted] and Embase	Hand search	N/A	01.05.2024
Alzheimer's Parkinson's Disease (AD/PD)	2021: https://cslide.ctimeetingtech.com/adpd21/attendee/confcal 2022: https://cslide.ctimeetingtech.com/adpd22/attendee/confcal/session/calendar/2022-03-15 2023: https://cslide.ctimeetingtech.com/global_storage/media/content/adpd23/ADPD23_-Posters for website Mar 29.pdf	Hand search	N/A	01.05.2024

Conference	Source of abstracts	Search strategy	Words/terms searched	Date of search
	2024: https://cslide.ctimeetingtech.com/adpd24/attendee/confcal/session/list			

Abbreviations: N/A = Not applicable

J.1.2 Search strategies

The search used a reproducible and validated search strategy. A combination of Emtree subject headings (Embase®), MeSH (medical subject headings, PubMed®), and free-text terms was used to retrieve all the relevant publications. The key biomedical databases, including Medical Literature Analysis and Retrieval System Online (MEDLINE®), MEDLINE in-process (searched via PubMed), Excerpta Medica Database (Embase®), and the Cochrane Central Register of Controlled Trials (CENTRAL) via the Cochrane Library, were searched for this literature review (Table 104, Table 105,Table 106). PubMed was searched to identify In-process citations, which provide records for articles before those records are indexed with MeSH or converted to out-of-scope status. "Ahead of Print" citations that precede the article's final publication in a MEDLINE indexed journal were also searched in PubMed.

Table 104 Search strategy for Embase.com

No.	Query	Results
#1	'disease exacerbation'/mj OR 'illness trajectory'/mj OR 'disease course'/mj OR 'probability'/mj	55,535
#2	((progress* OR conversion) NEAR/3 rate*):ti	2,222
#3	((transition* OR progress*) NEAR/3 probabilit*):ti	385
#4	((disease OR illness) NEAR/3 (progress* OR trajectory)):ti	20,114
#5	(transition* NEAR/3 disease):ti	413
#6	(disease NEAR/3 course*):ti	4,202
#7	(course NEAR/3 illness):ti	559
#8	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7	75,509
#9	'mild cognitive impairment'/mj OR mci:ti	17,212
#10	((mild* OR early* OR preclinical OR 'pre clinical') NEAR/2 ('cognitive impairment' OR 'cognitive impairments' OR 'cognitive impaired' OR 'cognitive dysfunction' OR 'cognitive decline')):ti	15,397
#11	'alzheimer disease'/mj OR alzheimer*:ti	150,024
#12	'dementia'/mj OR 'senile dementia'/mj OR 'mental deterioration'/mj OR 'pick presenile dementia'/mj OR 'presenile dementia'/mj OR 'senility'/mj OR 'tauopathy'/mj OR dementia*:ti	105,113
#13	#9 OR #10 OR #11 OR #12	246,041
#14	#8 AND #13	2,367
#15	('animal'/exp OR 'nonhuman'/exp) NOT 'human'/exp	7,764,264

#16	'editorial'/exp OR 'erratum'/de OR 'letter'/exp OR editorial:it	2,301,355
#17	#15 OR #16	9,992,247
#18	#14 NOT #17	2,066
#19	'clinical dementia rating scale sum of boxes'/exp OR 'clinical dementia rating scale sum of boxes':ti,ab OR 'cdr sb':ti,ab OR cdrsb:ti,ab OR 'cdr sob':ti,ab OR cdrsob:ti,ab	1,158
#20	'clinical dementia rating scale sum of boxes'/exp OR 'clinical dementia rating scale sum of boxes':ti,ab OR 'cdr sb':ti,ab OR cdrsb:ti,ab OR 'cdr sob':ti,ab OR cdrsob:ti,ab OR 'mini mental state examination'/exp OR 'mini-mental state exam*':ti,ab OR mmse:ti,ab	64,053
#21	'clinical dementia rating scale sum of boxes'/exp OR 'clinical dementia rating scale sum of boxes':ti,ab OR 'cdr sb':ti,ab OR cdrsb:ti,ab OR 'cdr sob':ti,ab OR cdrsob:ti,ab OR 'mini mental state examination'/exp OR 'mini-mental state exam*':ti,ab OR mmse:ti,ab OR 'clinical dementia rating'/exp OR 'clinical dementia rating':ti,ab OR cdr:ti,ab OR 'adcs mci adl*':ti,ab OR 'adcs adl mci*':ti,ab	74,024
#22	#19 OR #20 OR #21	74,024
#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

Table 105 Search strategy for Cochrane Library

No.	Query	Results
1	MeSH descriptor: [Disease Progression] explode all trees	9,455
2	MeSH descriptor: [Probability] this term only	3,956
3	(progress* NEAR/3 rate*):ti	196
4	(conversion NEAR/3 rate*):ti	36
5	(transition* NEAR/3 probabilit*):ti	6
6	(progress* NEAR/3 probabilit*):ti	2
7	(disease NEAR/3 progress*):ti	1,462
8	(illness NEAR/3 progress*):ti	8
9	(disease NEAR/3 trajectory):ti	3
10	(transition* NEAR/3 disease):ti	15
11	(disease NEAR/3 course*):ti	155
12	(illness NEAR/3 trajectory):ti	0
13	(course NEAR/3 illness):ti	41
14	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13	14,763
15	MeSH descriptor: [Cognitive Dysfunction] this term only	3,012

16	mci:ti	497
17	((mild* OR early* OR preclinical OR pre-clinical) NEAR/2 ((cognitive NEXT impair*) or "cognitive dysfunction" OR "cognitive decline")):ti	2,437
18	MeSH descriptor: [Alzheimer Disease] this term only	5,353
19	Alzheimer*:ti	8,202
20	MeSH descriptor: [Dementia] this term only	3,893
21	dementia*:ti	7,634
22	#15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21	20,883
23	#14 AND #22	432
24	[mh "Mental Status and Dementia Tests"] OR ("Clinical Dementia Rating scale Sum of Boxes" OR CDR-SB OR CDRSB OR CDR-SOB OR CDRSOB):ti,ab	1,110
25	[mh "Mental Status and Dementia Tests"] OR ("Clinical Dementia Rating scale Sum of Boxes" OR CDR-SB OR CDRSB OR CDR-SOB OR CDRSOB OR "mini-mental state exam" OR "mini-mental state examination" OR mmse):ti,ab	8,950
26	[mh "Mental Status and Dementia Tests"] OR ("Clinical Dementia Rating scale Sum of Boxes" or CDR-SB OR CDRSB OR CDR-SOB OR CDRSOB OR "mini-mental state exam" OR "mini-mental state examination" OR mmse OR "Clinical Dementia Rating" OR CDR OR ADCS-MCI-ADL* OR ADCS-ADL-MCI*):ti,ab	9,502
27	#24 OR #25 OR #26	9,502
28	#23 AND #27	153
29	#23 with Cochrane Library publication date to November 2018	306
30	#28 with Cochrane Library publication date from November 2018 to February 2020	10
31	#28 with Cochrane Library publication date from February 2020 to June 2021	3
32	#28 with Cochrane Library publication date from June 2021 to August 2023	17
33	#29 OR #30 OR #31 OR #32	336

Table 106 Search strategy for PubMed

No.	Query	Results
#1	“disease progression”	268,062
#2	“probability*”	281,333
#3	((progress* OR conversion) AND rate*)[Title]	309,800
#4	((transition* OR progress*) AND probabilit*)[Title]	28,709
#5	((disease OR illness) AND (progress* OR trajectory))[Title]	832,133
#6	(transition* AND disease)[Title]	81,716
#7	(disease AND course*)[Title]	282,332
#8	(course AND illness)[Title]	37,432
#9	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8	1,562,725

#10	“cognitive dysfunction”	52,484
#11	“mci”[Title]	1,383
#12	((mild* OR early* OR preclinical OR “pre clinical”) AND (“cognitive impairment” OR “cognitive impairments” OR “cognitive impaired” OR “cognitive dysfunction” OR “cognitive decline”))[Title]	48,494
#13	“alzheimer disease” OR alzheimer*[Title]	140,528
#14	“dementia” OR dementia*[Title]	170,965
#15	#10 OR #11 OR #12 OR #13 OR #14	306,738
#16	#9 AND #15	55,890
#17	(“animal” OR “nonhuman”) NOT “human”	1,243,264
#18	“editorial” OR “comment” OR “letter” OR “clinical-conference”	2,340,118
#19	#17 OR #18	3,558,094
#20	#16 NOT #19	50,952
#21	“Mental Status and Dementia Tests” OR (“Clinical Dementia Rating scale Sum of Boxes” OR CDR-SB OR CDRSB OR CDR-SOB OR CDRSOB)[Title/Abstract]	3,480
#22	“Mental Status and Dementia Tests” OR (“Clinical Dementia Rating scale Sum of Boxes” OR CDR-SB OR CDRSB OR CDR-SOB OR CDRSOB OR “mini-mental state exam*” OR mmse)[Title/Abstract]	30,154
#23	“Mental Status and Dementia Tests” OR (“Clinical Dementia Rating scale Sum of Boxes” OR CDR-SB OR CDRSB OR CDR-SOB OR CDRSOB OR “Mini-mental state Exam*” OR MMSE OR “Clinical Dementia Rating” OR CDR OR “ADCS-MCI-ADL*” OR “ADCS-ADL-MCI*”)[Title/Abstract]	38,631
#24	#21 OR #22 OR #23	38,631
#25	#20 AND #24	4,593
#26	#20 Filters: English, from 1964/1/1 – 2018/11/1	1,127
#27	#25 Filters: English, from 2018/11/1 – 2020/2/1	44
#28	#25 Filters: English, from 2020/2/1 – 2021/6/27	108
#29	#25 Filters: English, (inprocess[sb] OR pubstatusaheadofprint))	42
#30	#26 OR #27 OR #28 OR #29	1,321

J.1.3 Systematic selection of the studies

Initial screening of the retrieved citations was undertaken based on the title and abstract. Citations that did not match the eligibility criteria were excluded at this ‘first pass’ stage. If there was lack of clarity on whether citations were eligible for the review due to limited information in the abstract, these citations were included for ‘second pass’ stage. Two independent reviewers screened all citations and full text papers and any discrepancies in their decisions were resolved by a third reviewer. Citation duplicates (due to the overlap in the coverage of the databases) were also excluded at this stage. Upon acceptance during the initial screening, full-text copies of all references that could potentially meet the eligibility criteria were retrieved.

The full-text publications of all citations of potential interest were then screened for inclusion. Two independent reviewers screened all citations and full text papers and any

discrepancies in their decisions were resolved by a third reviewer. Citations that did not match the eligibility criteria were excluded at this 'second-pass' stage. At the full text screening stage, if there was lack of clarity on whether the publication met the eligibility criteria, these citations were excluded. Full-text screening was followed by linking of multiple publications. Studies meeting the eligibility criteria at the second screening stage were extracted.

The inclusion and exclusion criteria was further refined for Danish adaption

Table 107 Inclusion and exclusion criteria used for assessment of studies

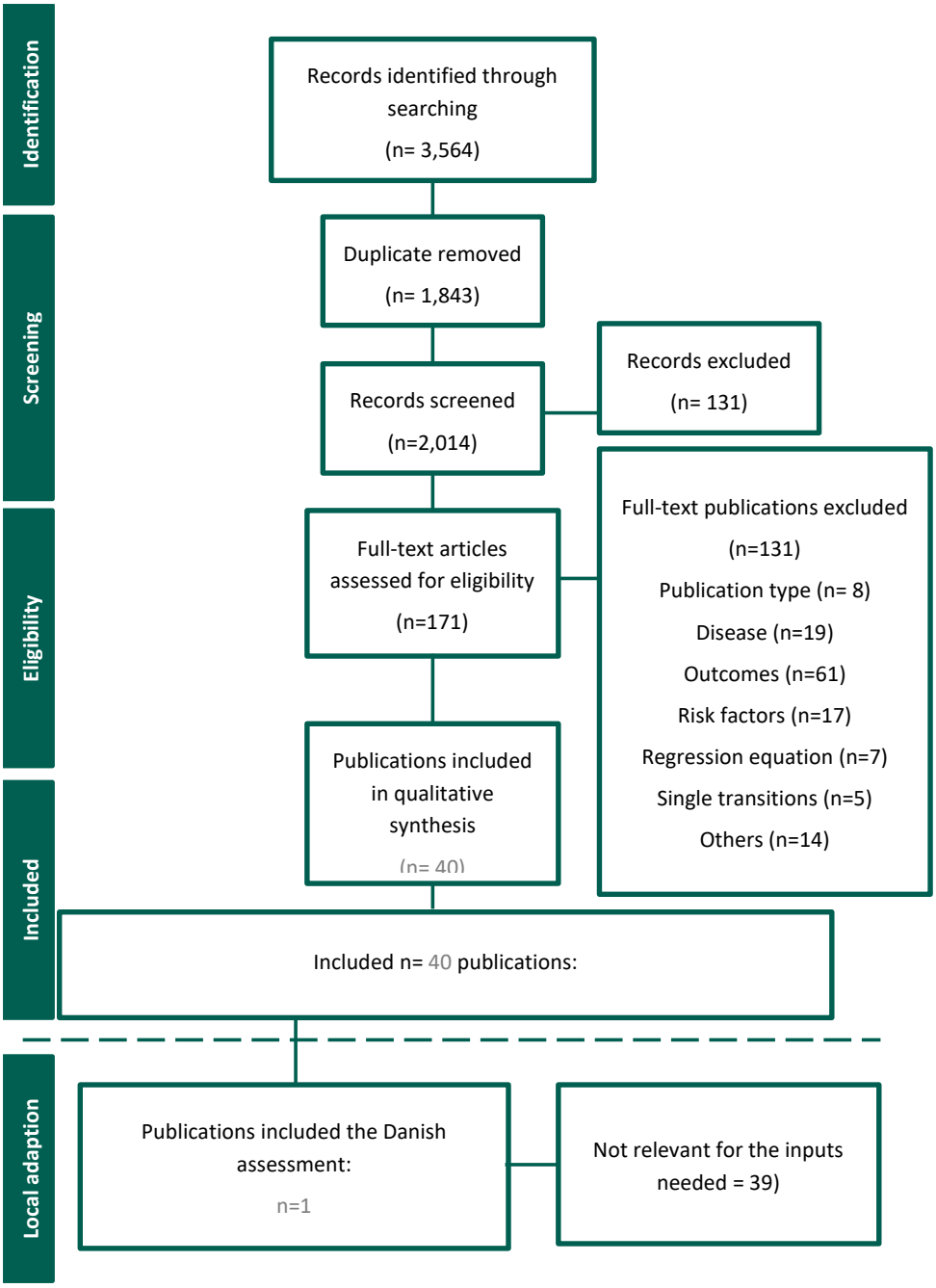
Clinical effectiveness	Inclusion criteria	Exclusion criteria	Changes, local adaption
Population	Disease: Patients with MCI (irrespective of causality) and/or AD (irrespective of severity) Age: Adult (≥18 years) patients Race: No restriction Gender: No restriction	Disease: Patients with a specific type of dementia other than AD, e.g., Parkinson's, vascular dementia, or frontotemporal dementia Age: Studies evaluating children Race: N/A Gender: N/A	N/A
Intervention	No restrictions	N/A	N/A
Comparators	No restrictions	N/A	N/A
Outcomes	Studies that solely or partially evaluated disease progression Natural disease progression as reported using MMSE or CDR-SB or ADAS-Cog Annual rates of change or transition probabilities for the entire study population, not just the subgroups	• Studies that did not report disease progression rates, conversion rates, or transition probabilities	The study to be leverage in the economic model was selected based on several factors as alignment with model structure and inputs need.
Study design/publication type	Study design: No restriction, all the interventional and observational studies will be considered for inclusion. Publication type: Peer-reviewed journal articles and conference abstracts Editorials, newspaper articles, book sections, letter,	Study design: N/A Publication type: Editorials, newspaper articles, book sections, letter, expert opinion or commentary, trial	N/A

	expert opinion or commentary, trial protocols, and reviews	protocols, and reviews	
Language restrictions	English language	Non-English	N/A
Time frame	Database inception to August 31st, 2023	N/A	N/A
Others	N/A	Studies conducted in-vitro and animals • Studies using a qualitative data collection method only, i.e., no quantitative measure • Studies were excluded if they focused on the development and validation of HRQoL instruments	N/A

Abbreviations: AD = Alzheimer's disease; MCI = Mild cognitive impairment, N/A = Not applicable

The literature search yielded 3,564 separate references. Following the first pass of the publications, 171 potentially relevant publications were identified. Full-text reports of these publications were retrieved for a more detailed evaluation. In total, 40 studies were identified.

Figure 33 PRISMA flow chart



AD: Alzheimer's disease; HRQoL, Health related quality of life; MCI: Mild cognitive impairment; RCT: Randomised controlled trial

15.1.2 Excluded full text references

The reference included in Table 100Table 108 in addition to Potashman et al., 2023 were included in the global SLR. For the local adaptation, only Potashman et al., 2023 was leveraged in the economic analysis.

Table 108 Overview of excluded studies

Reference	Reason for exclusion
Egan, M. F., Kost, J., Voss, T., Mukai, Y., Aisen, P. S., et al. (2019). Randomized Trial of Verubecestat for Prodromal Alzheimer's Disease. New England Journal of Medicine 380(15): 1408-1420	Not relevant
Green, C., Handels, R., Gustavsson, A., Wimo, A., Winblad, B., et al. (2019). Assessing cost-effectiveness of early intervention in Alzheimer's disease: An open-source modeling framework. Alzheimers Dement 15(10): 1309-1321	Not relevant
Hazen, J., Vistnes, M., Barca, M. L., Eldholm, R. S., Persson, K., et al. (2020). The Association Between Circulating Inflammatory Markers and the Progression of Alzheimer Disease in Norwegian Memory Clinic Patients With Mild Cognitive Impairment or Dementia. Alzheimer Dis Assoc Disord 34(1): 47-53.	Not relevant
Kim, Y. J., Cho, S.-K., Kim, H. J., San Lee, J., Lee, J., et al. (2019). Data-driven prognostic features of cognitive trajectories in patients with amnestic mild cognitive impairments. Alzheimer's research & therapy 11(1): 1-9.	Not relevant
Rosenberg, A., Solomon, A., Jelic, V., Hagman, G., Bogdanovic, N., et al. (2019). Progression to dementia in memory clinic patients with mild cognitive impairment and normal β-amyloid. Alzheimer's research & therapy 11(1): 1-12.	Not relevant
Schneider, L. S., Geffen, Y., Rabinowitz, J., Thomas, R. G., Schmidt, R., et al. (2019). Low-dose ladostigil for mild cognitive impairment: A phase 2 placebo-controlled clinical trial. Neurology 93(15): e1474-e1484	Not relevant
Shaw, L. M., Blennow, K., Buck, K., Eichenlaub, U., Lifke, V., et al. (2019). P3-267: ANALYSIS OF CEREBROSPINAL FLUID (CSF) BIOMARKERS TO PREDICT RISK OF CLINICAL DECLINE AND PROGRESSION TO DEMENTIA IN PATIENTS WITH MILD COGNITIVE IMPAIRMENT AND MILD COGNITIVE SYMPTOMS. Alzheimer's & Dementia 14(7S_Part_22): P1178-P1179.	Not relevant
Bloudek, L. M., Spackman, D. E., Veenstra, D. L. and Sullivan, S. D. (2011). CDR state transition probabilities in Alzheimer's disease with and without cholinesterase inhibitor intervention in an observational cohort. J Alzheimers Dis 24(3): 599-607.	Not relevant
Davis, M., T, O. C., Johnson, S., Cline, S., Merikle, E., et al. (2018). Estimating Alzheimer's Disease Progression Rates from Normal Cognition Through Mild Cognitive Impairment and Stages of Dementia. Curr Alzheimer Res 15(8): 777-788.	Not relevant
Green, C. and Zhang, S. (2016). Predicting the progression of Alzheimer's disease dementia: A multidomain health policy model. Alzheimers Dement 12(7): 776-785.	Not relevant
Hadjichrysanthou, C., Ower, A. K., de Wolf, F. and Anderson, R. M. (2018). The development of a stochastic mathematical model of Alzheimer's disease to help improve the design of clinical trials of potential treatments. PLoS One 13(1): e0190615	Not relevant

Shim, S. M., Song, J., Kim, J. H. and Jeon, J. P. (2016). Conversion pattern and predictive factor of mild cognitive impairment in elderly Koreans. Arch Gerontol Geriatr 64: 146-150.	Not relevant
Spackman, D. E., Kadiyala, S., Neumann, P. J., Veenstra, D. L. and Sullivan, S. D. (2012). Measuring Alzheimer disease progression with transition probabilities: estimates from NACC-UDS. Curr Alzheimer Res 9(9): 1050-1058	Not relevant
Yu, H. M., Yang, S. S., Gao, J. W., Zhou, L. Y., Liang, R. F., et al. (2013). Multi-state Markov model in outcome of mild cognitive impairments among community elderly residents in Mainland China. Int Psychogeriatr 25(5): 797-804	Not relevant
Yu, Lei, et al. "A nonstationary Markov transition model for computing the relative risk of dementia before death." Statistics in medicine 29.6 (2010): 639-648.	Not relevant
Zhang, L., Lim, C. Y., Maiti, T., Li, Y., Choi, J., et al. (2019). Analysis of conversion of Alzheimer's disease using a multi-state Markov model. Statistical methods in medical research 28(9): 2801-2819.	Not relevant
Lu, X., Chen, J., Shu, H., Wang, Z., Shi, Y. M., et al. (2020). Predicting conversion to Alzheimer's disease among individual high-risk patients using the Characterizing AD Risk Events index model. CNS Neurosci Ther 26(7): 720-729.	Not relevant
Platero, C. and Tobar, M. C. (2020). Longitudinal survival analysis and two-group comparison for predicting the progression of mild cognitive impairment to Alzheimer's disease. J Neurosci Methods 341: 108698	Not relevant
Teng, L., Li, Y., Zhao, Y., Hu, T., Zhang, Z., et al. (2020). Predicting MCI progression with FDG-PET and cognitive scores: a longitudinal study. BMC Neurol 20(1): 148.	Not relevant
Chen, X. R., Shao, Y. and Sadowski, M. J. (2021). Segmented Linear Mixed Model Analysis Reveals Association of the APOEε4 Allele with Faster Rate of Alzheimer's Disease Dementia Progression. Journal of Alzheimer's Disease (2021) 82:3 (921-937).	Not relevant
Kim, K. W., Woo, S. Y., Kim, S., Jang, H., Kim, Y., et al. (2020). Disease progression modeling of Alzheimer's disease according to education level. Sci Rep 10(1): 16808	Not relevant
Dyer, A. H., Murphy, C., Lawlor, B., Kennelly, S. P. and For The Nilvad Study, G. (2021). Long-term antipsychotic use and cognitive decline in community-dwelling older adults with mild-moderate Alzheimer disease: Data from NILVAD. Int J Geriatr Psychiatry	Not relevant
Mouchet, J., Betts, K. A., Georgieva, M. V., Ionescu-Ittu, R., Butler, L. M., et al. (2021). Classification, Prediction, and Concordance of Cognitive and Functional Progression in Patients with Mild Cognitive Impairment in the United States: A Latent Class Analysis. Journal of Alzheimer's Disease(Preprint): 1-16.\	Not relevant
Kuang, J., Zhang, P., Cai, T., Zou, Z., Li, L., et al. (2021). Prediction of transition from mild cognitive impairment to Alzheimer's disease based	Not relevant

on a logistic regression–artificial neural network–decision tree model. Geriatrics & Gerontology International 21(1): 43-47	
Lladó, A., Froelich, L., Khandker, R. K., Roset, M., Black, C. M., et al. (2021). Assessing the Progression of Alzheimer's Disease in Real-World Settings in Three European Countries. Journal of Alzheimer's Disease(Preprint): 1-11	Not relevant
Popescu, S. G., Whittington, A., Gunn, R. N., Matthews, P. M., Glocker, B., et al. (2020). Nonlinear biomarker interactions in conversion from mild cognitive impairment to Alzheimer's disease. Human brain mapping 41(15): 4406-4418.	Not relevant
Tabatabaei-Jafari, H., Shaw, M. E., Walsh, E. and Cherbuin, N. (2020). Cognitive/Functional Measures Predict Alzheimer's Disease, Dependent on Hippocampal Volume. J Gerontol B Psychol Sci Soc Sci 75(7): 1393-1402	Not relevant
Zhu, Y., Kim, M., Zhu, X., Kaufer, D. and Wu, G. (2021). Long range early diagnosis of Alzheimer's disease using longitudinal MR imaging data. Med Image Anal 67: 101825	Not relevant
Potashman, M., Buessing, M., Benea, M.L., Cummings, J., Borson, S., Pemberton-Ross, P., Epstein, A.J. (2021). Estimating Progression Rates Across the Spectrum of Alzheimer's Disease for Amyloid-Positive Individuals Using National Alzheimer's Coordinating Center Data. Neurol Ther 10(2): 941-953	Not relevant
Tahami Monfared A.A., Fu S., Hummel N., Qi L., Chandak A., Zhang R., Zhang Q. (2023a). Estimating Transition Probabilities Across the Alzheimerâ€™s Disease Continuum Using a Nationally Representative Real-World Database in the United States. Neurology and Therapy 12:4 (1235-1255).	Not relevant
Liu S., Cao, Y., Liu, J., Ding, X., Coyle, D. (2023). A novelty detection approach to effectively predict conversion from mild cognitive impairment to Alzheimer's disease. International Journal of Machine Learning and Cybernetics 14:213-228.	Not relevant
Rye I., Vik A., Kocinski M., Lundervold A.S., Lundervold A.J. (2022). Predicting conversion to Alzheimer's disease in individuals with Mild Cognitive Impairment using clinically transferable features. Scientific reports 12(1): 15566	Not relevant
Silva-Spanloa A., Lima M., LeitÃ£o M.J., Bernardes C., DurÃ£es J., Duro D., TÃ¡buas-Pereira M., Santana I., Baldeiras I. (2023). Blood biomarkers in mild cognitive impairment patients: Relationship between analytes and progression to Alzheimer disease dementia. European Journal of Neurology (2023) 30:6 (1565-1573).	Not relevant
Gueorguieva I., Chua L., Willis B.A., Sims J.R., Wessels A.M. (2023). Disease progression model using the integrated Alzheimer's Disease Rating Scale. Alzheimer's and Dementia (2023) 19:6 (2253-2264).	Not relevant
Saint-Jalmes M., Fedyashov V., Beck D., Baldwin T., Faux N.G., Bourgeat P., Fripp J., Masters C.L., Goudey B. (2023). Disease progression modelling of Alzheimer's disease using probabilistic principal components analysis. NeuroImage (2023) 278 Article Number: 120279	Not relevant
Tahami Monfared A.A., Ye W., Sardesai A., Folse H., Chavan A., Aruffo E., Zhang Q. (2023b). A Path to Improved Alzheimer's Care: Simulating Long-	Not relevant

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Jamalian S., Dolton M., Chanu P., Ramakrishnan V., Franco Y., Wildsmith K., Manser P., Teng E., Jin J.Y., Quartino A., Hsu J.C. (2023). Modeling Alzheimer's disease progression utilizing clinical trial and ADNI data to predict longitudinal trajectory of CDR-SB. CPT: Pharmacometrics and Systems Pharmacology (2023) 12:7 (1029-1042).	Not relevant
Lombardi, G., Lombardi, N., Bettiol, A., Crescioli, G., Ferrari, C., Lucidi, G., Polito, C., Berti, V., Bessi, V., Bagnoli, S., Nacmias, B., Vannacci, A., Sorbi S. (2022). Long-term use of pharmacological treatment in Alzheimer's disease: a retrospective cohort study in real-world clinical practice. Eur J Clin Pharmacol 78(7): 1155-1163	Not relevant
Voss T., Kost J., Mercer S.P., Furtek C., Randolph C., Lines C., Egan M.F., Cummings J.L. (2023). Progression from Prodromal Alzheimer's Disease to Mild Alzheimer's Disease Dementia in the Verubecestat APECS Study: Adjudicating Diagnostic Transitions. Journal of Alzheimer's Disease (2023) 92:1 (341-348).	Not relevant
Darmanthé N., Tabatabaei-Jafari H., Cherbuin N. (2021). Combination of plasma neurofilament light chain and mini-mental state examination score predicts progression from mild cognitive impairment to alzheimer's disease within 5 years. Journal of Alzheimer's Disease 82(3): 951-964	Not relevant

There is a limited body of high-quality longitudinal research that informs estimates of the natural history of Alzheimer's disease (AD) across its full clinical spectrum. Among the existing literature, only four studies (Potashman et al. (2021), Tahami Monfared et al. (2023a), Tahami Monfared et al. (2023b), and Davis et al. (2018)) have reported detailed TPs across AD stages studies (104-106, 156, 157).

Potashman et al. (2021) utilised patient-level longitudinal data from NACC database, focusing specifically on individuals confirmed to be amyloid beta-positive. The study derived annual TPs between clinically defined stages of AD—ranging from mild cognitive impairment (MCI) due to AD through to severe dementia—based on changes in CDR-SB. The analysis carefully accounted for covariates and focused on incident patients recently entering a stage, enhancing the reliability of progression estimates. The reported annual transition rates to more severe disease states were 21.8% from MCI to mild dementia, 35.9% from mild to moderate dementia, and 28.6% from moderate to severe dementia. Reverse transitions were also estimated, albeit with much lower probabilities, providing a comprehensive view of disease dynamics.

In contrast, Tahami Monfared et al. (2023a) employed a Markov model using data from the Health and Retirement Study, a nationally representative U.S. sample. AD stages in this study were identified using a modified version of the Telephone Interview for Cognitive Status, rather than biomarker confirmation. While the study estimated TPs across all stages of AD, the model reflected a broader, more heterogeneous population. TPs were generally lower than in Potashman et al., particularly in the earlier stages of disease, with only 12.8% transitioning from MCI to mild dementia in the first year, 5.0% from mild dementia due to AD to moderate dementia due to AD and less than 1% from moderate to severe dementia.

Tahami Monfared et al. (2023b) developed a disease simulation model to assess the long-term impact of lecanemab, an amyloid-targeting therapy, in combination with SoC versus SoC alone. This study also focused on patients with confirmed amyloid-beta pathology but limited its scope to early AD stages, specifically MCI and mild dementia. The findings demonstrated that lecanemab significantly delayed progression to more severe disease stages and institutionalisation.

Finally, Davis et al. (2018) also utilized NACC data to estimate annual progression rates between MCI and more severe stages of dementia. However, unlike Potashman, this study did not restrict its cohort to amyloid-positive individuals and lacked the same level of granularity in controlling for covariates or capturing reverse transitions.

Among these four studies, Potashman et al. (2021) was deemed to provide the most robust and comprehensive natural history estimates for Alzheimer's disease. It is the only study to cover the full clinical spectrum from MCI through severe dementia in a biomarker-confirmed (amyloid-positive) population, using well-validated clinical endpoints. The study's methodological rigor, combined with the biological specificity of the cohort, makes it the strongest available source for modelling natural disease AD progression in the economic analysis.

Table 109 Results from the search leveraged in this assessment

Reference	Study design	Patient population	Instrument
Potashman et al., 2021	Retrospective Longitudinal study, 12 years.	Patients with at least two visits observed in the NACC data, with a diagnosis of normal cognition at all visits or a diagnosis of MCI, dementia, or AD at any visit (Aβ+)	CDR measure generated from CDR-SB values

Abbreviations: Aβ+ = Amyloid beta positive; AD: Alzheimer's disease; CDR-SB = Clinical demetia rating – sum of boxes; MCI: Mild cognitive impairment; NACC = National Alzheimer's Coordinating Center

J.1.4 Quality assessment and generalizability of estimates

The findings of the Potashman et al. (2021) study may offer relevant insights for the Danish context. The study's focus on amyloid-positive individuals reflects a biologically grounded approach that aligns with contemporary understandings of Alzheimer's disease, with similar cognitive assessments and biomarker technologies. These commonalities in clinical practice and diagnostic infrastructure suggest a degree of comparability in how Alzheimer's disease is identified and staged across the two settings. Moreover, as a high-income country with well-developed healthcare systems, Denmark might structural characteristics with the USA that may support the applicability of disease progression models based on the NACC data.

That said, differences in healthcare delivery, population characteristics, and cultural context should be considered when considering the study's relevance. The NACC data is drawn from specialised research centres in the U.S., which may limit the generalisability of the results to the general population (American or Danish). Factors such as genetic background, lifestyle, education levels, and comorbid conditions could influence disease trajectories. While these considerations should be considered, the study was considered the most informative resource across the ones examined.

J.1.5 Unpublished data

N/A

Appendix K. Clarity AD Core Study: additional information

K.1 Summary of endpoints

A detailed description of the CDR-SB criteria is provided in Table 110.

Table 110 CDR-SB criteria

	Impairment				
	None	**Questionable**	**Mild**	**Moderate**	**Severe**
	0	**0.5**	**1**	**2**	**3**
Memory	No memory loss or slight inconsistent forgetfulness	Consistent slight forgetfulness; partial recollection of events; benign' forgetfulness	Moderate memory loss; more marked for recent events; defect interferes with everyday activities	Severe memory loss: only highly learned material retained; new material rapidly lost	Severe memory loss: only fragments remain
Orientation	Fully orientated	Full oriented expect for slight difficulty with time relationships	Moderate difficulty with time relationships; oriented for place at examination; may have geographic disorientation	Severe difficulty with time relationships; usually disoriented to time, often to place	Oriented to person only
Judgement & Problem Solving	Solves everyday problems & handles business & financial affairs well, judgment good in relation to past performance	Slight impairments in solving problems, similarities and differences	Moderate difficult in handling problems, similarities and differences; social judgement usually maintained	Severely impaired in handling problems, similarities and differences; social judgement usually impaired	Unable to make judgment or solve problems
Community Affairs	Independent Function at usual level in job, shopping, volunteer and social groups	Slight impairment in these activities	Unable to function independently at these activities although may still be engaged in some appears normal to casual	No pretense of independent function outside home	
				Appears well enough to be taken to functions	Appears too ill to be taken to functions

	Impairment				
	None 0	Questionable 0.5	Mild 1	Moderate 2	Severe 3
				outside a family home	outside a family home
Home & Hobbies	Life at home, hobbies and intellectual interests well maintained	Life at home hobbies and intellectual interests slightly impaired	Mild by definite impairment of function at home; more difficult chores abandoned; more complicated hobbies and interests abandoned	Only simple chores preserved very restricted interests, poorly maintained	No significant function in home
Personal Care	Fully capable of self-care	Need prompting	Requires assistance in dressing, hygiene, keeping of personal effects	Requires much help with personal care frequent incontinence	

CDR-SB = Clinical Dementia Rating Scale-Sum of Boxes
Source: Manning 2021 (158)

Table 111 presents a summary of the endpoints from the Core Study.

Table 111 Summary of scales used as endpoints in Clarity AD Core Study

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

CDR-SB (58)	Six domains:
	• Cognition:
	  ○ Memory
	  ○ Orientation
	  ○ Judgement/problem solving
	• Function:
	  ○ Community affairs
	  ○ Home/hobbies
	  ○ Personal care
		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. Moving from 0 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 (59).	Interview is administered by a qualified clinical professional, reported by the patient and study partner.

Secondary outcomes			
ADAS-Cog14 (61, 62)	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)	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 (62). 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,	Score is administered by clinician and includes both patient-completed tests and assessments observed by the clinician.

	• 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)	most severe and 0, least impairment). Typical range in early AD patients is 10 to 30.	
ADCS MCI-ADL (63)	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.
Exploratory outcomes:			

Global CDR (58)	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.

EQ-5D-5L (112)	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 (159, 160)	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 (161)	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 in 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 moderate burden. 41-60: moderate to severe burden. ≥ 61: severe burden.	Study partner.

Source: Clarity AD CSR (68)

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

K.2 Sensitivity and supplementary analyses

K.2.1 Description

The sensitivity analysis using log-transformed change from baseline in CDR-SB was performed using an MMRM to correct for possible skewness of data (68). The MMRM included log-transformed baseline CDR-SB as a covariate, with treatment group, visit, randomization stratification variables (i.e., clinical subgroup, use of AD symptomatic medication at baseline, APOE E4 carrier status, and geographical region), log-transformed baseline CDR-SB-by-visit, and treatment group-by-visit interaction as fixed effects (68). The following sensitivity analyses were conducted to assess the robustness of the primary analysis to missing data:

- Control-based multiple imputation approach with copy-increments using the actual value in placebo group was conducted. In this approach, all data in the placebo group were used to build the imputation model for each visit using a regression model. After the placebo imputation model was built, the increments (changes) between visits were used to impute missing values in the lecanemab group. For example, if the 6 months assessment in the lecanemab group was missing, the change between 3 months and 6 months was calculated from the placebo imputation model and that change was added to the value at 3 months in the lecanemab group to impute the value at 6 months in the lecanemab group.
- A control-based multiple imputation approach using the change from baseline by visit in the placebo group was conducted. In this approach, all data in the placebo group were used to build an imputation model for each visit using a regression model. After the placebo imputation model was built, the change from baseline value at a visit was used to impute missing values in the lecanemab group. For example, if 6 months assessment in the lecanemab group was missing, the change from baseline at 6 months was calculated from the placebo imputation model and that change from baseline at 6 months was used to impute the change from baseline at 6 months in the lecanemab group.

Additional sensitivity analyses were also performed:

- Repeated primary analyses using pure ITT patients (patients randomized and received at least one dose of medication) – per EMA request.

K.2.2 Results

K.2.2.1 CDR-SB

Sensitivity analyses were conducted to assess the robustness of the primary analysis to missing data; furthermore, supplementary analyses were also conducted (Table 112).

For reference, the first row “Base case MMRM” in are the results from the primary efficacy analysis described as per the study protocol of Clarity AD. The fourth row “Copy-Increments From Control based Multiple Imputation method” is the analysis that is presented in the EMA SmPC and represents the same population within the label of lecanemab. As can be seen, the results are consistent with the primary efficacy analysis, demonstrating the robustness of the primary analysis.

Table 112 Change from Baseline in CDR-SB at 18 Months – Sensitivity and Supplementary Analyses – Non-carriers and Heterozygotes

Type of sensitivity or supplementary analysis	Adjusted mean change from baseline Placebo	Adjusted mean change from baseline Lecanemab	Adjusted mean difference (95% CI); p-value
Base case MMRM **Analysis set = mITT**	[redacted]	[redacted]	[redacted]
MMRM with control-based imputation of missing data **Analysis set = mITT**	[redacted]	[redacted]	[redacted]
MMRM on all randomized subjects[a] **Analysis set = Randomized Set**	[redacted]	[redacted]	[redacted]
Copy-Increments From Control based Multiple Imputation method[b] **Analysis set = Randomized Set**	[redacted]	[redacted]	[redacted]
Control-Based Multiple Imputation method using change from baseline by visit[c] **Analysis set = Randomized Set**	[redacted]	[redacted]	[redacted]

Source: Eisai DOF (Appendix1 Table 14.2.1.2.52.7e) (162); Eisai DOF (Table 14.2.1.2.24nh) (163); Eisai DOF (110); Clarity AD CSR (68); EMA SmPC (1, 164)
Abbreviations: CDR-SB = Clinical Dementia Rating-Sum of Boxes; mITT = Modified Intent to Treat; MMRM = Mixed Model for Repeated Measures.
a All randomized subjects [redacted] are included.
b Control-based multiple imputation approach with copy-increments using the actual value in placebo group: All data in the placebo group were used to build the imputation model for each visit using a regression model. After the placebo imputation model was built, the changes between visits were used to impute missing values in the lecanemab group.
c Control-based multiple imputation approach using change from baseline by visit in the placebo group: All data in the placebo group were used to build an imputation model for each visit using a regression model. After the placebo imputation model was built, the change from baseline value at a visit was used to impute missing values in the lecanemab group.

K.2.2.2 ADAS-Cog14

Sensitivity analyses were conducted to assess the robustness of the secondary analysis to missing data (Table 113).

For reference, the first row “Base case MMRM” in Table 113 are the results from the secondary efficacy analysis described as per the study protocol of Clarity AD. The second row “Copy-Increments From Control based Multiple Imputation method” is the analysis that is presented in the EMA SmPC and represents the same population within the label of lecanemab. As can be seen, the results from the sensitivity analysis are consistent with the secondary efficacy analysis, demonstrating the robustness of the primary analysis.

Table 113 Change from Baseline in ADAS-Cog14 at 18 Months – Sensitivity Analyses, ApoE ε4 Non-carriers and Heterozygotes

Type of sensitivity or supplementary analysis	Adjusted mean change from baseline Placebo	Adjusted mean change from baseline Lecanemab	Adjusted mean difference (95% CI); p-value
Base case MMRM **Analysis set = mITT**	[redacted]	[redacted]	[redacted]
Copy-Increments From Control based Multiple Imputation method[a] **Analysis set = Randomized Set**	[redacted]	[redacted]	[redacted]

Source: Eisai DOF (Table 14.2.2.2.2nh) (83); Perry et al., 2024 (88); EMA SmPC (1)
Abbreviations: ADAS-Cog14 = Alzheimer's Disease Assessment Scale – Cognitive Subscale 14; mITT: Modified Intent to Treat; MMRM: Mixed Model for Repeated Measures.
a Control-based multiple imputation approach with copy-increments using the actual value in placebo group: All data in the placebo group were used to build the imputation model for each visit using a regression model. After the placebo imputation model was built, the changes between visits were used to impute missing values in the lecanemab group.

K.2.2.3 ADCS MCI-ADL

Sensitivity analyses were conducted to assess the robustness of the secondary analysis to missing data (Table 114).

For reference, the first row "Base case MMRM" in Table 16 are the results from the secondary efficacy analysis described as per the study protocol of Clarity AD. The second row "Copy-Increments From Control based Multiple Imputation method" is the analysis that is presented in the EMA SmPC and represents the same population within the label of lecanemab. As can be seen, the results from the sensitivity analysis are consistent with the secondary efficacy analysis, demonstrating the robustness of the primary analysis.

Table 114 Change from Baseline in ADCS MCI-ADL at 18 Months – Sensitivity Analyses, ApoE ε4 Non-carriers and Heterozygotes

Type of sensitivity or supplementary analysis	Adjusted mean change from baseline Placebo	Adjusted mean change from baseline Lecanemab	Adjusted mean difference (95% CI); p-value
Base case MMRM **Analysis set = mITT**	[redacted]	[redacted]	[redacted]
Copy-Increments From Control based Multiple Imputation method[a] **Analysis set = Randomized Set**	[redacted]	[redacted]	[redacted]

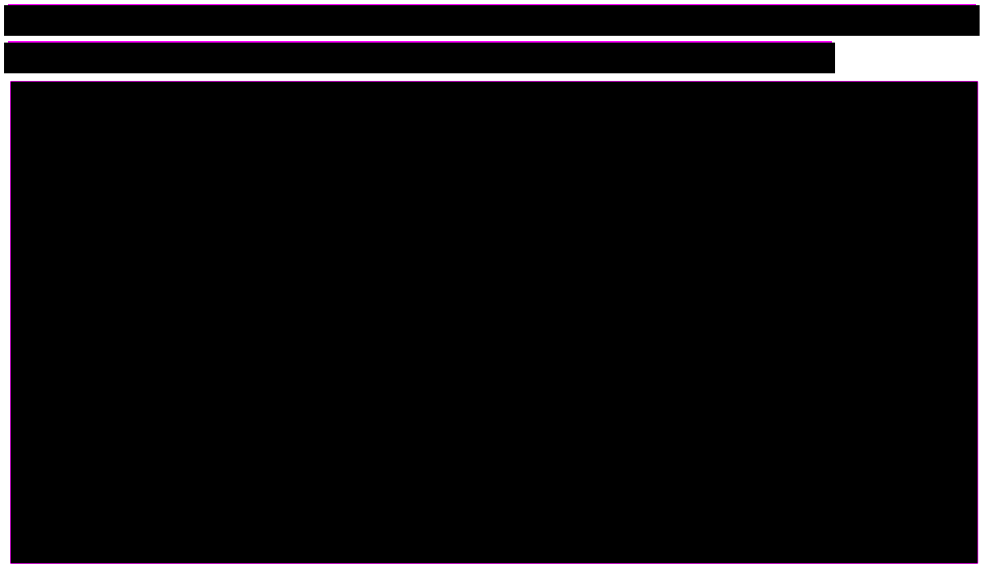
Source: Eisai DOF (Table 14.2.2.2.2nh) (83); Perry et al., 2024 (88); EMA SmPC (1)
Abbreviations: ADCS MCI-ADL = Alzheimer's Disease Cooperative Study-Activities of Daily Living Scale for Mild Cognitive Impairment; mITT: Modified Intent to Treat; MMRM: Mixed Model for Repeated Measures.
a Control-based multiple imputation approach with copy-increments using the actual value in placebo group: All data in the placebo group were used to build the imputation model for each visit using a regression model. After the placebo imputation model was built, the changes between visits were used to impute missing values in the lecanemab group.

K.3 Primary outcome

K.3.1 CDR-SB – Subgroup analysis

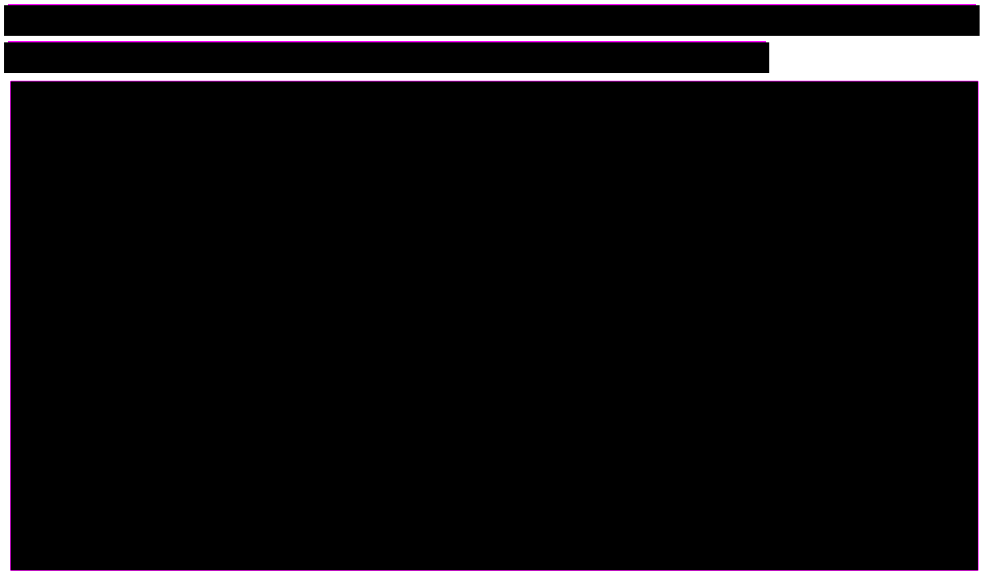
The effect of lecanemab in slowing cognitive and functional decline was also observed across subgroups, as presented in Figure 34, Figure 35, and Figure 36. In Clarity AD, randomization was stratified by use of symptomatic AD medication at baseline (yes/no), clinical subgroup (MCI due to AD, mild AD dementia), ApoE ε4 carrier status (carriers, non-carriers), and geographical region (North America, Europe, Asia). Intrinsic factors such as age, sex, race, and ApoE ε4 genotype were not randomization strata, and interaction terms were not statistically significant. These subgroup analyses were not powered to show statistical significance and results should therefore be interpreted with caution, and in the appropriate context.

Patients assigned to lecanemab experienced clinical benefit regardless of their baseline AD dementia stage (MCI due to AD, mild AD), use of AD symptomatic medication, ApoE ε4 status, age, sex, race, and geographical region (83).



Source: Eisai DOF (Table 14.2.1.1.2nh) (83); Eisai DOF (165)
Abbreviations: AD = Alzheimer's disease; ApoE ε4 = Apolipoprotein E4; CDR-SB = Clinical Dementia Rating Sum of Boxes; CI = Confidence Interval; MCI = Mild Cognitive Impairment
Note: N shows the number of subjects who are included in MMRM and is the same across all visits.

Source: Eisai DOF (Table 14.2.1.1.2nh) (83); Eisai DOF (165)
Abbreviations: AD = Alzheimer's disease; ApoE ε4 = Apolipoprotein E4; CDR-SB = Clinical Dementia Rating Sum of Boxes; CI = Confidence Interval; mTT = Modified intention-to-treat (FAS+)
Note: N shows the number of subjects who are included in MMRM and is the same across all visits.



Source: Eisai DOF (Table 14.2.1.1.2nh) (83); Eisai DOF (165)
Abbreviations: AD = Alzheimer's disease; ApoE ε4 = Apolipoprotein E4; CDR-SB = Clinical Dementia Rating Sum of Boxes; CI = Confidence Interval; mTT = Modified intention-to-treat (FAS+)
Note: N shows the number of subjects who are included in MMRM and is the same across all visits.

K.4 Exploratory outcomes

K.4.1 TTW of CDR-SB at 18 months

Subgroup analyses by AD dementia stage were conducted for TTW of CDR-SB score in ApoE ε4 non-carriers and heterozygotes. In patients with MCI due to AD, lecanemab showed a [redacted] reduction in the risk of progression to the next stage of AD on the CDR-SB score

[redacted] Figure 37) (97). A larger reduction of [redacted] was observed in patients with mild AD [redacted] Figure 38) (97).

[redacted]

Source : Eisai DOF (Time to worsening_nh_Core) (97)
Abbreviations: AD = Alzheimer's disease; ApoE ε4 = Apolipoprotein E4; CDR-SB = Clinical Dementia Rating Sum of Boxes; MCI = Mild cognitive impairment.

[redacted]

Source : Eisai DOF (Time to worsening_nh_Core) (97)
Abbreviations: AD = Alzheimer's disease; ApoE ε4 = Apolipoprotein E4; CDR-SB = Clinical Dementia Rating Sum of Boxes.

K.4.2 TTW of Global CDR at 18 months

Progression was defined as the Global CDR score progressing from 0.5 (MCI) to 1 (mild AD), or 1 (mild AD) to 2 (moderate AD). Progression to the next global CDR stage (e.g., moving from MCI to mild AD, or mild AD to moderate or severe AD) represents a clinically meaningful change since each stage represents greater loss of function and increasing

dependence on caregivers. The hazard ratio of disease progression to the next stage of AD, based on the global CDR score, was [redacted] showing lecanemab treatment reduced the risk of progression by [redacted] (Figure 39) (88). This time to event analysis demonstrated that patients receiving lecanemab experience a delay in disease progression and remain in earlier stages of AD for a longer period of time, even within the 18-month timeframe of the study.

At three months, [redacted] of lecanemab-treated patients who were ApoE ε4 non-carriers and heterozygous carriers had experienced a worsening of global CDR, 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 (83).

[redacted]

Source: Perry et al., 2024 (88)
Abbreviation: AD = Alzheimer's disease; ApoE ε4 = Apolipoprotein 4; CDR = Clinical Dementia Rating
Note: Progression was defined as Global CDR Score progressing from 0.5 [MCI] to 1 [mild AD dementia] or 1 [mild dementia] to 2 [moderate dementia]

A subgroup analyses by AD dementia stage was conducted for TTW of global CDR score in ApoE ε4 non-carriers and heterozygotes. In patients with MCI due to AD (Figure 40), lecanemab showed a [redacted] reduction in the risk of progression to the next stage of AD on the global CDR score [redacted] at 18 months (97). A larger reduction of [redacted] was observed in patients with mild AD (Figure 41) [redacted] (97).

[redacted]

Source : Eisai DOF (Time to worsening_nh_Core) (97)
Abbreviations: AD = Alzheimer's disease; ApoE ε4 = Apolipoprotein E4; CDR = Clinical Dementia Rating; MCI = Mild cognitive impairment.

[redacted]

Source : Eisai DOF (Time to worsening_nh_Core) (97)
Abbreviations: AD = Alzheimer's disease; ApoE ε4 = Apolipoprotein E4; CDR = Clinical Dementia Rating.

K.4.3 HRQoL

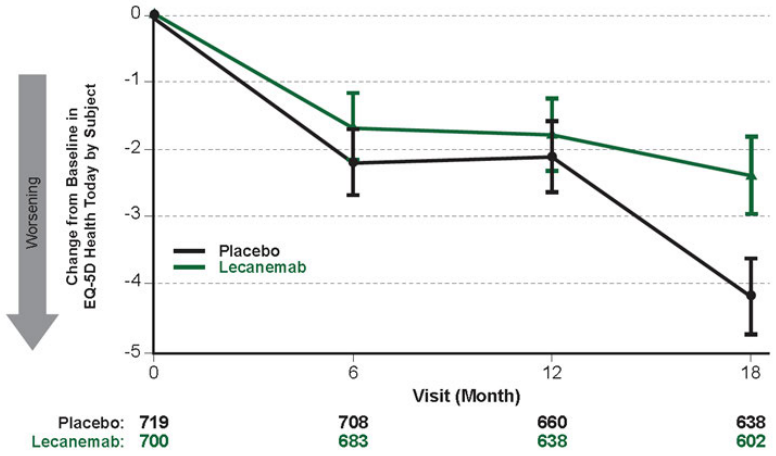
K.4.3.1 EQ-5D-5L

K.4.3.1.1 Patient-reported

The adjusted mean change of the EQ-5D-5L Health Today score was [redacted] in the lecanemab group and [redacted] in the placebo group, resulting in a statistically significant difference of [redacted] at 18 months (95% CI: [redacted] favouring lecanemab. This result represents [redacted] less decline in quality of life in the lecanemab group as compared to placebo, at 18 months (Figure 42). Lecanemab treatment was associated with a relative preservation of subject reported HRQoL versus placebo as shown by the adjusted mean difference at 18 months (88, 166).

When analysing the effect of lecanemab in individual domains, lecanemab was favoured in the three most relevant domains, anxiety/depression, self-care, and usual activities (Figure 43). Of note, the domains which did not favour lecanemab are not relevant in the symptomatology of early AD (89).

Figure 42 Change in Patient-Reported EQ-5D-5L (Health Today) Score up to 18 Months from Baseline in Clarity AD (Full Analysis Set+), ApoE ε4 Non-carriers and Heterozygotes



Source: Perry 2024 et al. (88)
Abbreviations: AD = Alzheimer's Disease; ApoE ε4 = Apolipoprotein E4; EQ-5D-5L = European QoL – 5 Dimensions – 5 Levels; SE = Standard Error

[redacted]

Source: Eisai DOF (89)
Abbreviations: AD = Alzheimer's Disease; ApoE ε4 = Apolipoprotein E4; CI = Confidence Interval; EQ-5D-5L = European QoL – 5 Dimensions – 5 Levels

K.4.3.1.2 Partner as a proxy

Even though the change from baseline in EQ-5D-5L Health Today Score did not have a statistically significant difference between the placebo and lecanemab groups in the Partner as a Proxy Results, an absolute difference was observed, with an adjusted mean difference between treatment groups of [redacted] less decline, [redacted] (166).

K.4.3.1.3 Partner results

Change from baseline in EQ-5D-5L Health Today Score did not have a statistically significant difference between the placebo and lecanemab groups in the Partner Survey Results, with an adjusted mean difference of [redacted] (166).

K.4.3.2 QOL-AD

K.4.3.2.1 Patient-reported

The adjusted mean change of the QOL-AD Subject's Survey score was [redacted] in the lecanemab group and [redacted] in the placebo group, resulting in a statistically significant difference of [redacted] at 18 months (95% CI: [redacted] favouring lecanemab. This result represents a [redacted] decreased decline in the lecanemab group as compared to placebo at 18 months (Figure 44). These results show that patients receiving lecanemab experienced a significantly smaller decline in their QOL-AD total score compared to those who received placebo (88, 167).

In the Subject's survey, the effect of lecanemab was consistent across most QOL-AD domains including less decline in the 'ability to do chores' (54.3%), 'ability to do things' (37.0%), 'friends' (53.0%), and 'life as a whole' (72.6%) (Figure 45) (89).

[redacted]

Source: Perry 2024 et al. (88)
Abbreviations: AD = Alzheimer's Disease; ApoE ε4 = Apolipoprotein E4; QoL-AD = Quality of Life – Alzheimer's Disease; SE = Standard Error

[redacted]

Source: Eisai DOF (89)
Abbreviations: AD = Alzheimer's Disease; ApoE ε4 = Apolipoprotein E4; CI = Confidence Interval; QOL-AD = Quality of Life in Alzheimer's Disease

K.4.3.2.2 Partner as a proxy

While no statistical significance was observed in the caregiver's proxy survey of QOL-AD at 18 months, an absolute difference between the treatment groups was observed, with an adjusted mean difference between lecanemab and placebo of [redacted] less decline, [redacted] (167).

K.4.3.3 ZBI

A statistically significant difference from baseline to 18 months was observed between lecanemab and placebo for the ZBI total score (adjusted mean treatment difference [redacted] less decline) (Figure 46) (168). A [redacted] reduction in decline suggests that lecanemab treatment delays some of the caregiving

burden for caregivers of patients with AD. This can lead to improved mental and emotional health of caregivers, reduced caregiver burnout, and enhanced family dynamics (168).

Of note, the effect of lecanemab was consistent across most ZBI domains (Figure 47) (89). Lecanemab benefit was seen across all 22 items of the ZBI, which includes caregiver-focused items such as: not having enough time, enough money, enough privacy, feeling one's social life has suffered, feeling embarrassed by one's loved ones, and having lost control of one's life.

[redacted]

Source: Perry 2024 et al. (88)
Abbreviations: AD = Alzheimer's Disease; ApoE ε4: Apolipoprotein E4; SE = Standard Error; ZBI = Zarit Burden Interview

[redacted]

Source: Eisai DOF (89)
Abbreviations: AD = Alzheimer's Disease; ApoE ε4 = Apolipoprotein E4; CI = Confidence Interval; ZBI = Zarit Burden Interview

K.4.4 Rate of change over time and time-saved analyses

K.4.4.1 CDR-SB

The slowing of progression can also be translated into the time difference between treatment and placebo to reach a specified level of decline, or "time-saved" with treatment. This is a direct measure of the delay in clinical decline with treatment, representing an extension of the time patients can remain with preserved cognition, function, and independence.

In the ApoE ε4 non-carriers and heterozygotes time-saved analysis, at the 18-month timepoint, the rate of decline in CDR-SB for lecanemab versus placebo was associated with a treatment difference of [redacted] (169). This corresponds to a [redacted] slowing of progression on lecanemab annually (95% CI: [redacted] This separation indicates that cognition and function as assessed by CDR-SB is preserved by approximately [redacted] months on lecanemab as compared to placebo at 18 months. In other words, lecanemab-treated patients are at the same stage of progression after 18 months as placebo patients would be at [redacted] months (Figure 48). After extrapolating data further using a linear mixed effects model in a prespecified analysis, it was determined that lecanemab takes an additional [redacted] months to reach the clinical decline seen in the placebo group at 18 months, with a treatment difference of [redacted] points at [redacted] months (169).

Figure 48 Rate of Change Over Time in CDR-SB During Clarity AD (18 Months) and Extrapolated to 30 months (Full Analysis Set+), ApoE ε4 Non-carriers and Heterozygotes

Source: Eisai DOF (169)
Abbreviations: AD = Alzheimer's Disease; ApoE ε4 = Apolipoprotein E4; CDR-SB = Clinical Dementia Rating Sum of Boxes; M = Month
Linear mixed effects were used to analyse the rate of change from baseline in CDR-SB over time
Purple lines represent treatment difference between lecanemab and placebo in rate of change over time. Blue dotted lines represent delay in clinically meaningful worsening with lecanemab vs. placebo at 12 and 18 months

K.4.4.2 ADAS-Cog14

For ADAS-Cog14, there was a [redacted] annual slowing of progression with lecanemab treatment (95% CI: [redacted] compared to placebo (170). This

separation indicates that cognition as assessed by ADAS-Cog14 is preserved by approximately [redacted] months on lecanemab relative to placebo during the 18-month Core Study (Figure 49) (170). After extrapolating data further, lecanemab treated patients take an additional [redacted] months to reach the clinical decline observed with placebo at 18 months (mean change in ADAS-Cog14 of [redacted] (170). Increasing separation over time can be observed between the lecanemab and placebo groups (170).

[redacted]

Source: Eisai DOF (Table 14.2.3.10.1)(170)
Abbreviations: ADAS-Cog14 = Alzheimer's Disease Assessment Scale – Cognitive Subscale 14-item version; ApoE ε4 = Apolipoprotein E4

K.4.4.3 ADCS MCI-ADL

For ADCS-MCI-ADL, there was a [redacted] annual slowing of progression with lecanemab treatment (95% CI: [redacted] compared to placebo in ApoE ε4 non-carriers and heterozygotes (171). This separation indicates that function as assessed by ADCS-MCI-ADL is preserved by approximately [redacted] months with lecanemab relative to placebo during the 18-month Core (171). W After extrapolating data further, patients treated with lecanemab take an additional [redacted] months to reach the clinical decline seen with placebo at 18 months (mean change in ADCS-MCI-ADL of [redacted]50) (171). Increasing separation over time can be observed between the lecanemab and placebo groups (171).

[redacted]

Source: Eisai 2024 (171)
Abbreviations: ADCS-MCI-ADL = Alzheimer's Disease Cooperative Study–Activities of Daily Living Scale for Mild Cognitive Impairment; ApoE ε4 = Apolipoprotein E4

K.4.5 Progressor analyses

K.4.5.1 CDR-SB

Progressor analyses (also referred to as responder analyses) evaluating the proportion of subjects worsening by meaningful amounts or thresholds of clear clinical importance are a standard approach to support assessment of the clinical relevance of treatment effect sizes. Progressor analyses do this by incorporating a clinically relevant degree of disease progression at a subject-level.

A CDR-SB progressor analysis was conducted to evaluate a range of possible CDR-SB changes (incremental thresholds of worsening) at 18 months of lecanemab treatment versus placebo in ApoE ε4 non-carriers and heterozygotes (Figure 51). Lecanemab treatment results in the slowing of disease progression compared to placebo regardless of the cut-point applied from 0.5 to a 3-point or greater worsening, with a clinically meaningful relative risk reduction of progression for every threshold (172). The risk of the lecanemab treatment group experiencing cognitive and/or functional decline further decreased as the threshold increased. The risk of the lecanemab group worsening by 1-point or greater on CDR-SB was [redacted] lower than the placebo group, while the risk of the lecanemab group worsening by 3-points or greater on CDR-SB was reduced further to [redacted] when compared to the placebo group.

[redacted]

Source: Eisai DOF (172)
Abbreviations: AD = Alzheimer's disease; ApoE ε4 = Apolipoprotein 4; CDR-SB = Clinical Dementia Rating – Sum of Boxes; RR = Relative Risk
Note: ITT population, missing data handled through control-based imputation. RR = Relative Risk difference from placebo

K.4.5.2 ADAS-Cog14

An ADAS-Cog14 progressor analysis at 18 months was conducted in ApoE ε4 non-carriers and heterozygotes. A reduction was observed in the relative risk of cognitive decline with lecanemab treatment (1 to a 16-point worsening on ADAS-Cog14). The higher the threshold, the greater the reduction in the relative risk. At the threshold of a decline of 5 points or more, [redacted] of patients treated with placebo declined compared to [redacted] of patients treated with lecanemab, representing a [redacted] reduction in relative risk (Figure 53). A 5-point decline would generally reflect a subject deteriorating across multiple cognitive domains.

[redacted]

Source: Eisai DOF (172)
Abbreviations: ADAS-Cog14 = Alzheimer Disease Assessment Scale-Cognitive subscale 14-item version; ApoE ε4 = Apolipoprotein E4, ITT = Intent to treat; RR = Relative risk
Note: ITT population, missing data handled through control-based imputation. RR = Relative Risk difference from placebo

K.4.5.3 ADCS MCI-ADL

An ADCS-MCI-ADL progressor analyses at 18 months was conducted in ApoE ε4 non-carriers and heterozygotes. A reduction was observed in the relative risk of cognitive decline with lecanemab treatment (-1 to a -7-point worsening on ADCS-MCI-ADL). The higher the threshold, the greater the reduction in the relative risk. At the threshold of a decline of -5 or more, [redacted] of patients treated with placebo declined compared to [redacted] of patients treated with lecanemab, representing a [redacted] reduction in relative risk [redacted] A 5-point decline would generally reflect a subject deteriorating across multiple daily activities (173)

[redacted]

Source: Eisai DOF (172)
Abbreviations: ADAS-Cog14 = Alzheimer Disease Assessment Scale-Cognitive subscale 14-item version; ApoE ε4 = Apolipoprotein E4, ITT = Intent to treat; RR = Relative risk
Note: ITT population, missing data handled through control-based imputation. RR = Relative Risk difference from placebo

K.5 Biomarker outcomes

The biomarker-related outcomes in Clarity AD reflect robust target engagement (brain Aβ removal). Significantly, further downstream effects were observed in the slowing of the accumulation of tau, the pathology that is most closely associated with cognitive symptoms of the disease and also the strongest predictor of disease progression (174).

K.5.1 Amyloid PET SUVR composite at 18 months

Two tracers (florbetaben and florbetapir) were used in the amyloid positron emission tomography (PET) imaging substudy. For both tracers, there was a statistically significant difference between the placebo group and lecanemab group in the change in amyloid PET standardised uptake value ratio (SUVR) at 18 months in ApoE ε4 non-carrier and heterozygotes patients (

Table 115) (83).

Table 115 Biomarkers of Amyloid PET SUVr During Clarity AD (18 months) (PD Analysis Set), ApoE ε4 Non-carriers and Heterozygotes

Subgroups	Lecanemab	Placebo
Amyloid PET SUVr (florbetaben)		
N analysed	[redacted]	[redacted]
n analysed	[redacted]	[redacted]
Mean change from baseline (SE)	[redacted]	[redacted]
Mean difference, (95% CI); p-value	[redacted]	
Amyloid PET SUVr (florbetapir)		
N analysed	[redacted]	[redacted]
n analysed	[redacted]	[redacted]
Mean change from baseline (SE)	[redacted]	[redacted]
Mean difference, (95% CI); p-value	[redacted]	

Source: Eisai DOF (Table 14.2.7.1.2nh) (83)
Abbreviations: ApoE ε4 = Apolipoprotein E4; PD = Pharmacodynamic; PET = Positron Emission Tomography; SE = Standard error; SUVr = standardized uptake value ratio
N shows the number of subjects who are included in MMRM and is the same across all visits. n shows the number of subjects at 18 months.

K.5.2 Tau PET SUVR at 18 months

The tau PET SUVR results were dependent on the region of observation and concordant with what is expected for early stages of disease progression. In a brain region not considered to be relevant to early AD pathology (whole cortical grey matter region of interest (ROI)), There was no statistically significant difference in the change from baseline in the tau PET SUVR at 18 months for lecanemab versus placebo in ApoE ε4 non-carriers and heterozygotes. (83). When focusing specifically in brain areas involved in early AD pathology (175, 176), a statistically significant decrease was observed at 18 months in favour of lecanemab in the medial temporal ROI (adjusted mean treatment difference [redacted] as measured by tau PET SUVR (83).

Table 116 Biomarkers of Tau PET SUVr During Clarity AD (18 months) (PD Analysis Set), ApoE ε4 Non-carriers and Heterozygotes

Subgroups	Lecanemab	Placebo
Tau PET SUVr (Whole Cortical Gray Matter Region)		
N analysed	[redacted]	[redacted]
n analysed	[redacted]	[redacted]
Mean change from baseline (SE)	[redacted]	[redacted]
Mean difference, (95% CI); p-value	[redacted]	
Tau PET (Medial Temporal Region)		
N analysed	[redacted]	[redacted]
n analysed	[redacted]	[redacted]
Mean change from baseline (SE)	[redacted]	[redacted]
Mean difference, (95% CI); p-value	[redacted]	
Tau PET (Meta Temporal Region)		
N analysed	[redacted]	[redacted]

n analysed	[redacted]	[redacted]
Mean change from baseline (SE)	[redacted]	[redacted]
Mean difference, (95% CI); p-value	[redacted]	
Tau PET (Temporal Region)		
N analysed	[redacted]	[redacted]
n analysed	[redacted]	[redacted]
Mean change from baseline (SE)	[redacted]	[redacted]
Mean difference, (95% CI); p-value	[redacted]	

Source: Eisai DOF (Table 14.2.7.2.2nh) (83)
Abbreviations: ApoE ε4 = Apolipoprotein E4; PD = Pharmacodynamic; PET = Positron Emission Tomography; SE = Standard error; SUVr = standardized uptake value ratio
N shows the number of subjects who are included in MMRM and is the same across all visits. n shows the number of subjects at 18 months.

K.5.3 Plasma and CSF Biomarkers at 18 months

Plasma and CSF Aβ42/40

Lecanemab showed statistically significant increases in both plasma Aβ42/40 (adjusted mean difference: [redacted] and cerebrospinal fluid (CSF) Aβ42 (adjusted mean difference: [redacted] compared with placebo at 18 months in ApoE ε4 non-carriers and heterozygotes (Table 118) (83).

Table 117 Biomarkers of Amyloid Beta (Plasma Aβ42/40 & CSF Aβ42) During Clarity AD (18 months) (PD Analysis Set), ApoE ε4 Non-carriers and Heterozygotes

Subgroups	Lecanemab	Placebo
Plasma Aβ42/40		
N analysed	[redacted]	[redacted]
n analysed	[redacted]	[redacted]
Mean change from baseline (SE)	[redacted]	[redacted]
Mean difference, (95% CI); p-value	[redacted]	
CSF Aβ42		
N analysed	[redacted]	[redacted]
n analysed	[redacted]	[redacted]
Mean change from baseline (SE)	[redacted]	[redacted]
Mean difference, (95% CI); p-value	[redacted]	

Source: Eisai DOF (14.2.7.3.2nh) (83)
Abbreviations: Aβ = Amyloid beta; ApoE ε4 = Apolipoprotein E4; CSF = Cerebrospinal fluid; PD = Pharmacodynamic; SE = Standard error
N shows the number of subjects who are included in MMRM and is the same across all visits. n shows the number of subjects at 18 months.

Plasma and CSF ptau-181

Additional tau biomarkers include plasma ptau-181, which is elevated in early stages of AD and continues to increase as the disease progresses, and CSF ptau-181. Lecanemab demonstrated a statistically significant decrease in both plasma p-tau181 (adjusted treatment difference: [redacted] and CSF ptau-181 (adjusted treatment difference: [redacted] compared to placebo at 18 months in ApoE ε4 non-carriers and heterozygotes (83).

Table 118 Biomarkers of plasma and CSF ptau-181 During Clarity AD (18 months) (PD Analysis Set), ApoE ε4 Non-carriers and Heterozygotes

Subgroups	Lecanemab	Placebo
Plasma p-tau181		
N analysed	[redacted]	[redacted]
n analysed	[redacted]	[redacted]
Mean change from baseline (SE)	[redacted]	[redacted]
Mean difference, (95% CI); p-value	[redacted]	
CSF p-tau181		
N analysed	[redacted]	[redacted]
n analysed	[redacted]	[redacted]
Mean change from baseline (SE)	[redacted]	[redacted]
Mean difference, (95% CI); p-value	[redacted]	

Source: Eisai DOF (Table 14.2.7.3.2nh) (83)

Abbreviations: AD = Alzheimer's Disease; ApoE ε4 = Apolipoprotein E4; CSF = Cerebrospinal fluid; PD = Pharmacodynamic; PET = Positron Emission Tomography; p-tau = Phosphorylated-tau; SE = Standard error

N shows the number of subjects who are included in MMRM and is the same across all visits. n shows the number of subjects at 18 months.

Appendix L. Clarity AD OLE – additional information

L.1 Primary outcome

Similar to the ApoE ε4 noncarrier and heterozygote subpopulation, the treatment effect between lecanemab treatment and the natural history cohort continues to increase from 18 through 36 months (absolute treatment difference: -0.45 [18 months] vs. -0.95 [36 months]) in the full population, illustrating cumulative benefit from lecanemab treatment compared to natural disease progression (177). Note, the OLE period included patients who received SC lecanemab (as opposed to patients that received IV only), which is currently not an approved formulation within the current EMA label.

Figure 54 Mean Change from Baseline to 36 Months in CDR-SB with ADNI Matched Cohort (IV + SC) – 18 Months of Core Study + 18 Months of OLE (Full Analysis Set+), full population

Source: Eisai CTAD 2024 (177)
Abbreviations: ADNI = Alzheimer's Disease Neuroimaging Initiative; CDR-SB = Clinical Dementia Rating-sum of boxes; IV = intravenous; OLE = open-label extension; SC = subcutaneous; SE = standard error.
Note: Early start lecanemab 10 mg/kg biweekly group are those subjects on lecanemab 10 mg/kg biweekly in the Core. Delayed start LEC10-BW group (those subjects that initiate lecanemab 10 mg/kg biweekly in the OLE). OLE includes those participants on subcutaneous and intravenous formulations.
Based on testing the hypothesis that early start arm maintains at least half of the treatment effect seen at the end of 18 months. Based on modified intention-to-treat analysis population. Adjusted mean change from baseline, SE and p-value are derived using mixed model repeat measures (MMRM) with treatment group, visit, treatment group by visit interaction, clinical subgroup, use of Alzheimer's disease symptomatic medication at baseline, ApoE ε4 carrier status, region, baseline value by visit interaction as fixed effects, and baseline value as covariate.

L.2 Secondary outcomes

L.2.1 ADAS-Cog14

The adjusted mean change from baseline at 36 months in the ADAS-Cog14 score was [redacted] in the early starters and [redacted] in the delayed starters, representing an adjusted mean group difference of [redacted] (Figure 55). Separation between the early starters and delayed starters was maintained between 18 and 36 months when all subjects received lecanemab, with parallel disease trajectory observed between 18 to 36 months, illustrating all patients benefited from lecanemab treatment whether they started early or late, with more benefit gained when patients started the treatment early (178).

The absolute mean at 36 months for ADAS-Cog14 score in the early starters was [redacted] resulting in an absolute mean change from baseline of [redacted] (90).

Source: Eisai DOF (178)
Abbreviations: ADAS-Cog14 = Alzheimer's Disease Assessment Scale – Cognitive Subscale 14; ApoE ε4 = Apolipoprotein E4; CDR-SB = Clinical Dementia Rating Sum of Boxes; IV = Intravenous; OLE = Open-Label Extension; SE = Standard Error

L.2.2 ADCS MCI-ADL

The adjusted mean change from baseline at 36 months in the ADCS MCI-ADL score was - [redacted] in the early start lecanemab group and [redacted] in the delayed start lecanemab group, representing a statistically significant adjusted mean group difference of [redacted] between the early start and delayed start lecanemab groups (Figure 56) (178). Separation between the early start and delayed start was maintained between 18 and 36 months when all subjects received lecanemab, with parallel disease trajectory observed between 18 to 36 months illustrating all patients benefited from lecanemab treatment whether they started early or late, with more benefit gained when patients started the treatment early (178).

The absolute mean at 36 months for ADCS MCI-ADL score in the early starters was [redacted] resulting in an absolute mean change from baseline of [redacted] (90).

[redacted]

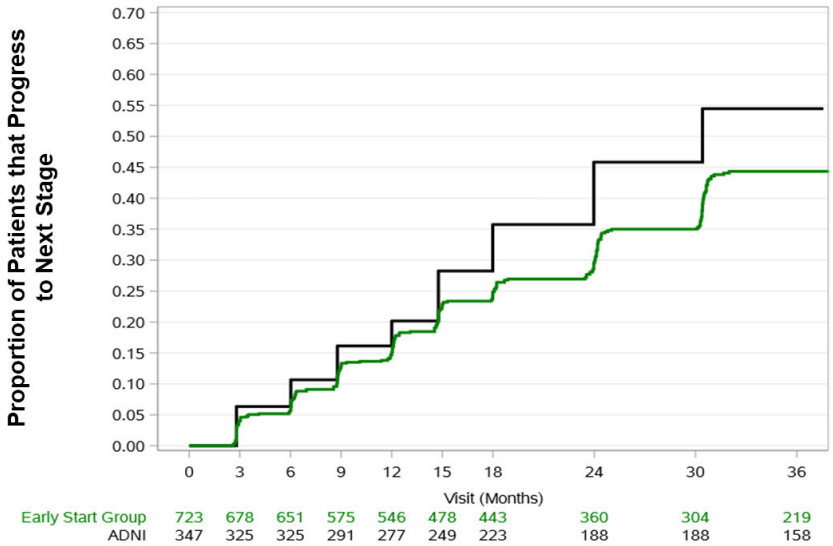
Source: Eisai DOF (178)
Abbreviations: ADCS-MCI-ADL = Alzheimer's Disease Cooperative Study-Activities of Daily Living Inventory Mild Cognitive Impairment Version; ApoE ε4 = Apolipoprotein E4; CDR-SB = Clinical Dementia Rating Sum of Boxes; IV = Intravenous; OLE = Open-Label Extension; SE: Standard Error

L.3 Exploratory outcomes

L.3.1 TTW of CDR-SB at 36 months

As shown in Figure 57, lecanemab meaningfully delayed progression (HR: 0.73 [95% CI: 0.60, 0.89]) to next AD stage as measured by CDR-SB score through 36 months in the ApoE ε4 non-carrier and heterozygotepopulation (88).

Figure 57 TTW on CDR-SB Score through 36 Months (IV Only); 18 Months; Core Study + 18 Months of OLE (FAS+), ApoE ε4 Non-carriers and Heterozygotes



Source: Perry 2024 et al. (88)
Abbreviations: ADCS-MCI-ADL = Alzheimer's Disease Cooperative Study-Activities of Daily Living Inventory Mild Cognitive Impairment Version; ApoE ε4 = Apolipoprotein E4; CDR-SB = Clinical Dementia Rating Sum of Boxes; IV: Intravenous; OLE = Open-Label Extension; SE = Standard Error
Note: Disease defined by CDR-SB (O'Bryant et al., 2008). Progression was defined as progressing from 0.5 [MCI] to 1 [mild AD dementia] or 1 [mild dementia] to 2 [moderate dementia]

L.3.2 TTW of CDR-SB at 48 months

As shown in Figure 58, lecanemab meaningfully continues to delayed progression (HR: 0.70 [95% CI: 0.58, 0.85]) to next AD stage as measured by CDR-SB score through 48 months in the ApoE ε4 non-carrier and heterozygote population (99).

Source: Eisai DOF (99)

L.3.3 HRQoL

L.3.3.1.1 EQ-5D-5L – patient-reported

Data on patient-reported EQ-5D-5L Health Today score associated with lecanemab treatment at 36 months versus placebo are shown in Figure 59. The adjusted mean change from baseline at 36 months for the EQ-5D-5L Health Today score was in the lecanemab (early start) group and in the placebo (delayed start) group, resulting in an adjusted mean difference of These data show consistent separation between the early start and delayed start lecanemab-treated ApoE ε4 non-carriers and heterozygote patients between 18 and 36 months, illustrating that there is increased preservation of HRQoL in patients who started lecanemab treatment early (179).

[redacted]

Source: Eisai DOF (179)
Abbreviations: AD: Alzheimer's Disease; ApoE ε4: Apolipoprotein E4; EQ-5D-5L: European QoL – 5 Dimensions – 5 Levels; SE: Standard Error

L.3.3.1.2 QOL-AD

Data on QOL-AD associated with lecanemab treatment at 36 months versus placebo are shown in Figure 60. The adjusted mean change from baseline at 36 months for the QOL-AD Subject's Survey score was [redacted] in the lecanemab (early start) group and [redacted] in the placebo (delayed start) group, resulting in an adjusted mean difference of [redacted] These data show consistent separation between the early start and delayed start lecanemab-treated ApoE ε4 non-carrier and heterozygote patients between 18 and 36 months, illustrating that that there is increased preservation of in patients who started lecanemab treatment early (179).

[redacted]

Source: Eisai DOF (179)

Abbreviations: AD = Alzheimer's Disease; ApoE ε4 = Apolipoprotein E4; QoL-AD = Quality of Life – Alzheimer's Disease; SE = Standard Error

L.3.3.1.3 ZBI

Data on ZBI associated with lecanemab treatment at 36 months versus placebo are shown in Figure 61. The adjusted mean change from baseline at 36 months in ZBI was [redacted] in the lecanemab (early start) group and [redacted] in the placebo (delayed start) group, resulting in an adjusted mean difference of [redacted] These data show consistent separation between the early start and delayed start lecanemab-treated ApoE ε4 non-carriers and heterozygote carrier patients between 18 and 36 months, illustrating that there is increased preservation of caregiver HRQoL when patients started lecanemab treatment early (179).

[redacted]

Source: Eisai DOF (179)
Abbreviations: AD = Alzheimer's Disease; ApoE ε4 = Apolipoprotein E4; SE = Standard Error; ZBI = Zarit Burden Interview

L.4 ADNI-matched cohort overview

The Alzheimer's Disease Neuroimaging Initiative (ADNI) study actively supports the investigation and development of treatments that slow or stop the progression of AD. The ADNI study tracks the progression of the disease using biological markers (biomarkers; for example, chemicals found in blood, or changes to the brain observed in MRI and PET scans), together with clinical measures (cognitive and neuropsychological tests), to assess the brain's structure and function over the course of three disease states (cognitively normal/unimpaired, mild cognitive impairment, dementia). Researchers at over 60 clinical sites in the USA and Canada collect data to study the progression of AD in the human brain across normal aging, MCI, and Alzheimer's disease and dementia. Thus, the patients in the ADNI cohort represent the population of North America. The main goals of the ADNI study are to improve how doctors diagnose patients with AD and to provide study data and biospecimens (samples) to qualified researchers worldwide (180).

As illustrated in Table 119, ADNI study began in 2004, with an initial 5-year phase, ADNI-1, which was set out to include a total of 800 participants with and without MCI or AD. Two subsequent phases followed: ADNI "Grand Opportunities" (ADNI-GO) and ADNI-2. ADNI-GO supported amyloid PET scans for ADNI-1 participants plus additional 200 early MCI participants. ADNI-2 further expanded the study population by 550 to include people with other forms of memory impairment such as late MCI. A 5-year renewal of ADNI-2, called ADNI-3, began in 2016 with a major goal of validating longitudinal tau PET imaging. ADNI is ongoing, currently in the ADNI-4 study phase (2022-2027)(181).

Table 119 Phases of ADNI

	ADNI-1	ADNI-GO	ADNI-2	ADNI-3	ADNI-4
Study Period	2004-2010	2009-2011	2011-2016	2016-2022	2022 and beyond
Study Duration	5 years	2 years	5 years	5 years	5 years
Cohort	200 elderly controls 400 MCI 200 AD	Existing ADNI1 + 200 early MCI	Existing ADNI1 and ADNI-GO 150 elderly controls 100 elderly MCI 150 late MCI 150 AD	Existing ADNI-1, ADNI-GO, ADNI-2 + 133 elderly controls 151 MCI 87 AD	Existing ADNI-1, ADNI-GO, ADNI-2, ADNI-3 + 200 elderly controls, 200 MCI, 100 AD/DEM
Primary Goal	Develop biomarkers as outcome measures for clinical trials	Examine biomarkers in earlier stages of disease	Develop biomarkers as predictors of cognitive decline, and as outcome measures	Study the use of tau PET and functional imaging techniques in clinical trials	Improve representation of historically underrepresented groups in AD research

Abbreviations: ADNI observational cohort vs. Clarity AD patient population

[redacted]

5. Baseline diagnosis:
   c. "MCI" with the global Clinical Dementia Rating (CDR) score=0.5 and CDR memory ≥0.5, or
   d. "AD" with global CDR=0.5 or 1.0 and CDR memory ≥0.5;
6. Proportion of MCI (60%) and mild AD (40%)
7. Baseline Mini–Mental State Exam (MMSE) score ≥22;
8. At least 1 of 2 criteria for amyloid positivity:

c. baseline amyloid PET standardized uptake value ratios (SUVr) florbetapir ≥1.11 or amyloid PET SUVr Pittsburgh compound B (PIB) ≥1.47, or
d. baseline cerebrospinal fluid (CSF) total tau/amyloid beta (Aβ) >0.222.

L.4.1 Methods

[redacted]

Table 120 Schedule of evaluations for subjects with MCI and subjects with Alzheimer's disease in ADNI

	Screening/ baseline visit	Month 6	Month 12	Month 18	Month 24	Month 30	Month 36
Mild Cognitive Impairment							
Clinical	X	X	X	X	X	NC	X
Telephone	X	X		X	X	NC	X
Alzheimer's disease							
Clinical	X	X	X		X	NC	
Telephone				X		NC	

Source: Petersen et al. 2010, Table 1

Abbreviations: MCI = mild cognitive impairment; ADNI = Alzheimer's Disease Neuroimaging Initiative; NC = not collected

The analyses of the change from baseline in CDR-SB and time-to worsening of CDR-SB were conducted on ApoE Ɛ4 non-carriers or heterozygotes. To run these analyses through 36 months (18 months of Core Study + 18 months of OLE), the ADNI observational cohort was restricted to include ApoE Ɛ4 non-carriers or heterozygotes only to match with the Clarity AD restricted population. As illustrated in Table 121, the majority of the ADNI data were collected from ADNI-1 and ADNI-2

Table 121 Break-down of ADNI-matched cohort, by ADNI Phase, ApoE Ɛ4 non-carriers or heterozygotes

	ADNI-matched cohort (N=346)
ADNI-1	
ADNI-2	
ADNI-3	

Source: data on file.

Baseline demographic and clinical characteristics between Clarity AD patient population and the ADNI-matched cohort are similar. There was no difference in the trend seen in patient profile between the overall population and the restricted population (Table 122).

Table 122 Baseline demographic and clinical characteristics – Clarity AD restricted population and ADNI-matched cohort

Category	Clarity AD Core Study Combined Total	ADNI-matched Cohort
N		
Age		
Mean (SD)		
Median		
ApoE Ɛ4 heterozygous carriers, n (%)		
Disease Stage, n (%)		
MCI		
Mild		
Baselines CDR-SB		
Mean (SD)		
Median		

Source: Data on file.
Abbreviations: AD, Alzheimer's disease; ADNI, Alzheimer's Disease Neuroimaging Initiative; APOE E4, apolipoprotein E4; CDR-SB, Clinical Dementia Rating – Sum of Boxes; MCI, mild cognitive impairment; SD, standard deviation

L.4.1.1 Adjusted mean change from baseline in CDR-SB in context of observational cohort through 36 months, ApoE Ɛ4 non-carriers and heterozygous carriers

L.4.1.1.1 Results

In the ApoE Ɛ4 heterozygote and non-carrier population, the absolute treatment difference between lecanemab early starters and the ADNI-matched cohort increases over time at 18 months, at 30 months, at 36 months; Table 121),

illustrating that lecanemab treatment results in cumulative benefit compared to natural disease progression. This analysis supports that slowing of disease progression seen at 18 months with lecanemab vs. placebo is maintained and continues to separate over time with continued treatment.

[redacted]

Source: Data on file.
Abbreviations: AD, Alzheimer's disease; ADNI, Alzheimer's Disease Neuroimaging Initiative; APOE E4, apolipoprotein E4; CDR-SB, Clinical Dementia Rating – Sum of Boxes; MCI, mild cognitive impairment; SD, standard deviation

Table 123 Adjusted Mean Change (±SE) from Baseline in CDR-SB in Context of Observational Cohort (ADNI) through 36 months, Clarity AD Core and OLE Phase, ApoE Ɛ4 heterozygotes and non-carriers

	18 Months		18 Months		30 Months		36 Months	
	Lecanemab	Placebo	Lecanemab early starters	ADNI matched cohort	Lecanemab early starters	ADNI matched cohort	Lecanemab early starters	ADNI matched cohort
Adjusted mean change								
Adjusted mean difference								
Absolute mean (SD)								
Absolute mean change from baseline*								
Absolute mean difference								

Source: Data on file; Eisai DOF (301COREOLE_36m_simple summary statistics indicated population) (90)

Note: *mean change from baseline for lecanemab early starters is based on the lecanemab baseline CD-SB score from the Core Study (3.17). Therefore, absolute mean change from baseline for lecanemab is calculated For the ADNI cohort, the adjusted mean change from baseline at 36 months is used.

Abbreviations: AD, Alzheimer's disease; ADNI, Alzheimer's Disease Neuroimaging Initiative; APOE E4, apolipoprotein E4; CDR-SB, Clinical Dementia Rating – Sum of Boxes; MCI, mild cognitive impairment; SD, standard deviation

L.4.1.2 TTW of CDR-SB

L.4.1.2.1 Methods

Survival analysis was conducted, with the aim of estimating the risk reduction in the TTW of CDR-SB. The worsening of CDR-SB was defined as the CDR-SB score increasing 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) based on the first worsening where a worsening is observed in 2 consecutive visits. Health states (MCI due to AD, mild AD, moderate AD, severe AD) were defined as per the economic model using CDR-SB (Table 124). TTW of CDR-SB was censored at the date of the last observed CDR-SB assessment in Clarity AD if a patient did not complete all scheduled assessments. Using the Clarity AD 36 months data (18 months of Core Study + 18 months of OLE), Cox proportional hazards model was used to calculate the hazard ratio for TTW of CDR-SB for lecanemab vs the ADNI-matched cohort, with clinical subgroup and ApoE ε4 carrier status included as covariates.

As CDR-SB data were collected less frequently in ADNI than in Clarity AD and inconsistently between MCI due to AD and mild AD (see the methods section for 'Adjusted mean change from baseline in CDR-SB in context of observational cohort through 36 months' for details), to conduct time to event analysis using the same rule described for the Clarity AD data (i.e., using 2 consecutive visit data to define "worsening"), missing data at post-baseline visits in ADNI were imputed using the multiple imputation approach (m=500 datasets) under missing at random (MAR) assumption. Hazard ratio was derived using Rubin's approach with multiple imputation.

Table 124 Health state definitions

Endpoint	MCI due to AD	Mild AD	Moderate AD	Severe AD
CDR-SB	0.5–4.0	4.5–9.0	9.5–15.5	16.0–18.0

Source: O'Bryant, 2008.
Abbreviations: AD= Alzheimer's disease; CDR= clinical dementia rating; CDR-SB= clinical dementia rating – sum of boxes; MCI= mild cognitive impairment.

L.4.1.2.2 Results

For ApoE Ɛ4 heterozygotes and non-carriers the treatment effect based on the time-to-worsening of CDR-SB by 36 months was similar to the effect observed in the Clarity AD Core Study (18 months). In the Clarity AD Core Study the hazard ratio for lecanemab vs placebo for TTW of CDR-SB was 0.698 (95% CI: 0.568, 0.858: p=0.00062), illustrating that lecanemab treatment reduced the risk of progression to the next stage of AD on the CDR-SB score by 30.2% at 18 months. The hazard ratio for TTW of CDR-SB was [redacted] for lecanemab vs the ADNI-matched control arm by 36 months. The assumption of proportional hazards was supported by plots of the log-cumulative hazard and tests of the scaled Schoenfeld residuals (Figure 64 and Figure 65).

[redacted]

Abbreviations: ADNI, Alzheimer's Disease Neuroimaging Initiative; CDR-SB, clinical dementia rating sum of boxes; KM = Kaplan-Meier OLE, open-label extension; SE, standard error, TTW = time to worsening.

[redacted]

[redacted]

Appendix M. Summary of the clinical meaningful benefit of lecanemab

AD progresses slowly at first; however, the rate of progression accelerates exponentially once past the early stages (183-185). Hence, lecanemab intervention while patients remain in the early stages of AD presents a critical opportunity to delay disease progression.

Patients with AD, their caregivers, and clinicians consistently highlight the importance of maintaining patients in the earlier stages of disease for longer where HRQoL and functional independence are maintained (186, 187). From their standpoint, there are several urgent treatment needs:

- Improving or maintaining core abilities of cognition, daily function, and behaviour, which become severely impaired over the course of the disease
- Slowing the disability associated with AD such that individuals remain at milder, less debilitating, and less costly stages
- Maintaining QoL for both the patient and caregiver(s), given that AD has an enormous detrimental impact on caregivers and often multiple family members, in addition to its impact on patients themselves

In the Clarity AD trial, lecanemab slowed the progression of AD as measured by established, validated, and globally accepted clinical endpoints that directly address the existing unmet needs in early AD:

- Slowing the cognitive and functional decline seen in early AD by 33.5%, based on CDR-SB score

- Slowing cognitive decline based on a 27.9% reduction in decline in ADAS-Cog14 score
- Slowing functional decline based on a 39.2% reduction in decline in ADCS MCI-ADL score
- Slowing the decline in QoL for patients:
    - [redacted] less decline by patient-reported EQ-5D-5L VAS subtotal
    - [redacted] less decline by patient reported QoL-AD
- Slowing the the increased caregiver burden associated with AD progression, based on [redacted] less decline in ZBI score.

Lecanemab also impacted the characteristic biomarkers of AD, such as amyloid, tau, neurodegeneration, and gliosis (neuroinflammation) biomarkers, providing a biological basis for the observed treatment effects (188).

The clinical scales used in Clarity AD were selected and agreed to by global Health Authorities as they are objective, validated, standardized, and sufficiently sensitive to detect changes over time in an investigational setting to support product registration. When these scales are used, clinicians can measure progression of 0.5 or 1.0 in any domain of the CDR-SB, and of 1 point on the ADAS-Cog14 and the ADCS-MCI-ADL, irrespective of whether a subject is on a treatment or not. The scales have a wide range that is intended to reflect the entire AD continuum from MCI due to AD through to severe dementia.

The population studied in Clarity AD was MCI due to AD and mild AD dementia, i.e., the earliest symptomatic stages of AD; therefore, only a portion of the scale ranges are relevant for the interpretation of clinical relevance in the early AD population (CDR-SB: 0.5 – 9.0, Table 14) (188). Additionally, the extent to which the placebo treatment arm progressed on each scale can serve as the threshold for the maximum amount to which the lecanemab treatment arm could expect to progress. In Clarity AD, the placebo arm progressed an average of 1.73 on CDR-SB over 18 months (5.845 on ADAS-Cog14, 5.703 on ADCS MCI-ADL).

The primary and key secondary analyses in Clarity AD establish the clinical benefit of lecanemab in early AD. The clinical relevance of the effect sizes observed at the group level is demonstrated by responder and time-to-event analyses. Specifically, TTW analysis confirms a delay in progression to the next more disabling stage of AD for lecanemab treated subjects (CDR-SB TTW; HR: 0.698, [redacted] (97). Furthermore, the proportion of subjects progressing by a meaningful extent establishes the clinical relevance of the group level effect. That is, there is a reduction in the proportion of patients progressing to a more debilitating AD stage on lecanemab, regardless of the threshold of decline selected.

Responder, time to event, and “time saved” analyses are a standard approach to establish the clinical relevance of the treatment effect and “can be used after statistical significance has been established on the mean level of the required primary variables” as confirmed in guidance from regulators (189). These analyses build the concept of clinical meaningfulness into the definition of worsening, describing the proportion of subjects who worsen by that meaningful amount. They help quantify and interpret how long a drug can delay or halt the progression of neurodegenerative diseases such as AD, as explicitly stated in EMA guidance (189):

"In a number of applications, for example those concerned with Alzheimer's disease or epileptic disorders, it is difficult to interpret small but statistically significant improvements in the mean level of the primary variables. For this reason, the term "responder" (and "non-responder") is used to express the clinical benefit of the treatment to individual patients…/…the "responder" analysis should be used in establishing the clinical relevance of the observed effect as an aid to assess efficacy and clinical safety."

Applying this guidance to the results of Clarity AD, the analyses demonstrate that regardless of the clinically meaningful threshold or milestone, and across multiple endpoints, lecanemab demonstrates consistent clinically relevant slowing of progression versus placebo.

Primary and key secondary clinical endpoints establish the clinical benefit of lecanemab in early AD

In the primary analysis evaluating CDR-SB, Clarity AD exceeded the prospectively defined target for the study with a treatment difference of -0.58 points on a scale up to 18 (89). The average baseline CDR-SB score was 3.17 in the lecanemab group and 3.22 in the placebo group, with the placebo group progressing by an average of 1.73 points over 18 months; therefore, it is not plausible to slow progression beyond 1.73 points at the group-level. This placebo decline is consistent with many other AD clinical trials and natural disease progression studies, validating the control arm of the study. Furthermore, the observed 33.5% reduced clinical decline from baseline in CDR-SB in the Clarity AD study is consistent with a clinically meaningful difference based on the AD peer-reviewed literature, statistical principles, and guidance from the regulatory authorities under which Clarity AD was designed (190-195).

An effect was seen on patients' symptoms across all CDR domains, including memory, orientation, judgment, community activities, hobbies, and personal care (89). For each domain, there are distinct thresholds marking transitions from 0 (unimpaired) through to 3 (severely impaired). Moving from 0 to 0.5 in any of the 6 domains represents a shift from unimpaired to impaired, while a shift from 0.5 to 1.0 means a change from impaired to dependent in that domain. Such changes are noticeable and relevant to patients and their caregivers. The CDR-SB with its combination of history-taking and testing-replicates the process used in clinical practice to detect important progression milestones.

Key secondary clinical endpoints included changes from baseline at 18 months in ADAS-Cog14 and ADCS-MCI-ADL.

- For ADAS-Cog14, the average baseline score was 24.48 points and 24.40 points for the lecanemab and placebo groups, respectively (83). Patients in the placebo group progressed an average of 5.845 points over 18 months; therefore, it is not plausible to slow progression beyond 5.845 points at the group-level (83). The mean lecanemab treatment difference was -1.633 points, equating to a 27.9% reduction in cognitive decline with lecanemab versus placebo (83). The ADAS-Cog14 total score is intended to capture the entire clinical course of AD (which can be longer than 10 years) and ranges from unimpaired (0) to severe cognitive impairment (90). The ADAS-Cog14 involves a direct assessment of the subject on 14 cognitive items assessing memory, orientation, language, executive function, and praxis (learned motor activity).

- For ADCS-MCI-ADL, the average baseline score was 41.3 points and 40.9 points for the lecanemab and placebo groups, respectively (83). Patients in the placebo group progressed an average -5.703 points over 18 months; therefore, it is not plausible to slow progression beyond 5.703 points at the group-level (83). The mean lecanemab treatment different was 2.234 points, equating to a 39.2% reduction at 18 months in the decline of daily functions (83). The ADCS-MCI-ADL is a scale developed to assess the level of functional integrity in early AD by assessing the extent to which the subject performs home and community activities (independently or requiring support), such as: finding personal belongings, using household appliances, cleaning, keeping appointments with friends, making phone calls, cooking meals, and managing money. A smaller number of items address basic self-maintenance activities (basic activities of daily living), such as dressing oneself. The informant/caregiver reports the patient's function observed over the previous 4 weeks. On an individual level, a single point change can mean a shift from performing an activity unsupervised to requiring supervision, or a shift from requiring supervision to requiring physical assistance by the caregiver. Such changes are noticeable and meaningful to subjects and their caregivers.

Lecanemab Delays Progression to the Next Stage of Disease

The global CDR score operationalises disease staging used in the clinical setting for dementia severity; therefore, worsening of this score represents progressing to later stages of dementia, which is an event of clear clinical importance and disruption to daily life (196). The global CDR score represents the following stages of disease: 0 = unimpaired; 0.5 = questionable impairment (MCI); 1, 2, 3 = mild, moderate, and severe dementia, respectively (196). These are well-established stages of clinical importance, representing the syndromal categorical staging in the NIA-AA criteria (23), FDA guidance on early AD (197), and revised AD diagnostic criteria ((198)). Delaying progression to the next global CDR stage represents a clinically meaningful change since moving from MCI to mild AD or mild AD dementia to moderate AD dementia impacts the management and treatment of patients with AD, and where each stage transition is relevant to subjects, caregivers and clinicians.

The TTW analysis on global CDR score was a prespecified responder-based analysis in the ITT population consistent with EMA guidance, demonstrating the clinical relevance of the group-level mean differences. TTW of a global CDR score was defined as time from randomisation to the time of worsening of the global CDR score (i.e., the first worsening where there is an increase from baseline on the global CDR score in two consecutive visits). The TTW HR of disease progression on the global CDR score is [redacted] representing a [redacted] lower risk of patients on lecanemab progressing to the next stage of disease on the AD continuum as compared to placebo (Figure 39). This time to event analysis demonstrates that lecanemab maintains subjects at an earlier stage of disease and delays disability from AD progression. It reinforces the clinical relevance of the primary outcome (which is also supported by key secondary endpoints, quality of life and biomarker outcomes).

Regardless of clinically meaningful threshold or milestone, lecanemab treatment shows consistent slowing of progression versus placebo

A responder analysis was conducted to assess the proportion of subjects in the placebo and lecanemab groups that progressed by increasing thresholds on the CDR-SB scale in Clarity AD by 18 months (Figure 51). The analysis was based on a combination of observed data and for data that were missing, a conservative control-based imputation (see Appendix K.2.1) was used so that a complete 18-month dataset could be used for every single subject in the study. Such analyses are appropriate from a clinical, statistical, and regulatory perspective, to provide interpretation of the group-level treatment effect. All multiplicity controlled prespecified analyses are highly statistically significant. As a drug effect has been established, the responder analyses do not need to follow Type 1 error control (189).

For CDR-SB, fewer lecanemab subjects declined compared to placebo, regardless of the threshold applied from 0.5 to a 3-point worsening. In Figure 51, the x-axis represents a range of possible CDR-SB changes by 18 months of treatment with each column providing incremental thresholds of worsening. The two left columns show all subjects and whether they had no decline or any decline. The bars represent the proportion of subjects that reached that level of decline or greater. There is a relative risk reduction of clinical decline with lecanemab treatment for every threshold. The higher the threshold, the greater the relative risk reduction.

For example, the middle column quantitates subjects that progressed by 1.5 or more on CDR-SB, since that represents the median decline for placebo, which also is in the range of a clinically meaningful decline according to MCID. A 1.5-point decline would generally reflect a subject deteriorating in more than one cognitive or functional CDR-SB domain. At this threshold, 53% of placebo subjects declined compared to 35% of lecanemab treated subjects. These results translate into meaningful relative risk reduction of clinical decline with lecanemab compared to placebo by 18 months for every threshold applied. This is a meaningful analysis since irrespective of selected threshold, lecanemab shows relative risk reduction versus placebo.

The results are consistent with those from similar analyses focussing on ADAS-Cog14 and ADCS-MCI-ADL (see Appendix K.4.5.2 and K.4.5.3).

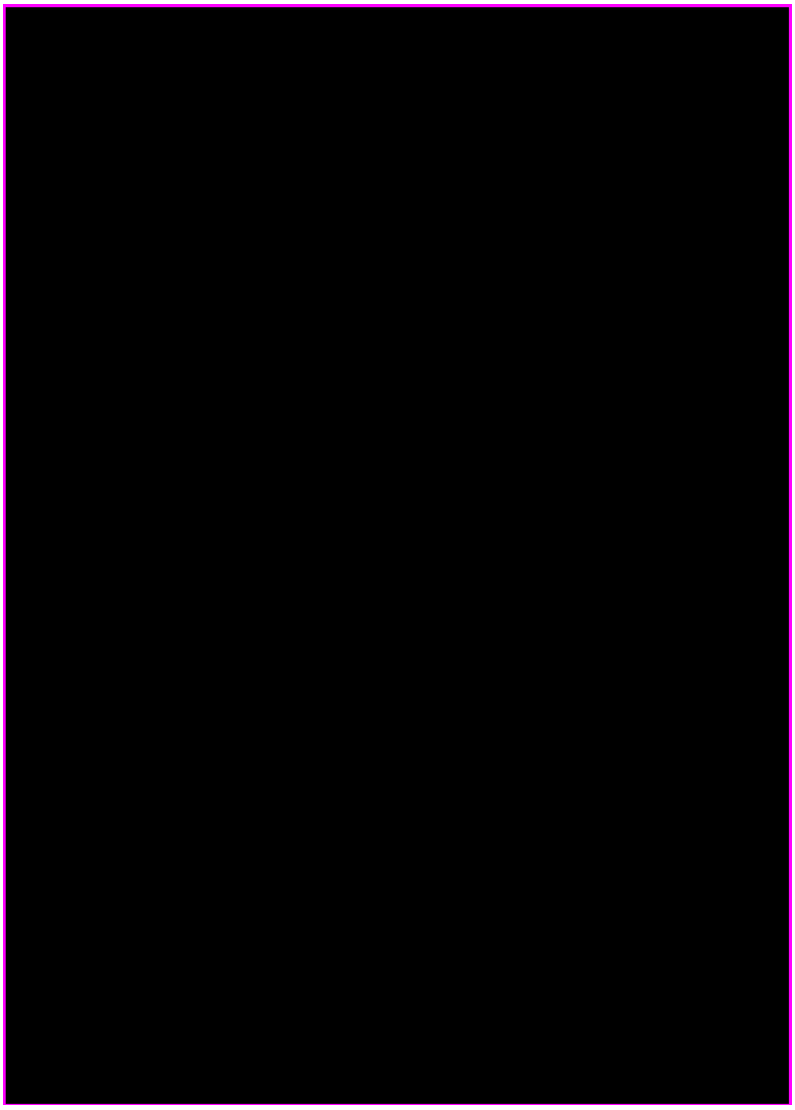
Time-saved analyses further support that lecanemab maintains subjects at earlier stages of disease for longer

The changes over 18 months on CDR-SB, ADAS-Cog14, and ADCS-MCI-ADL, can be interpreted as average time preserved/time-saved, whereby subjects are maintained at earlier stages of disease where they are able to function more independently, with better QoL.

From the time-saved LME analysis based on CDR-SB, (a prespecified analysis in the ITT population), there is increasing separation over time between placebo and lecanemab, with a [redacted] slowing of progression on lecanemab annually [redacted] versus placebo (Figure 48). This separation indicates that cognition and function (as assessed by CDR-SB) is preserved by approximately [redacted] months with lecanemab treatment relative to placebo during the 18-month Core Study. In other words, lecanemab-treated patients are able to maintain their cognitive and functional state for approximately [redacted] months longer than placebo treated patients.

This trend of increasing separation in CDR-SB scores over time in Clarity AD is consistent with hypotheses found within the AD literature, which states that initiating a hypothetical therapy targeting the underlying pathophysiology of early AD leads to a 20% to 30% slower decline compared with placebo, with the meaningful benefit accruing over time (Figure 66) (191, 192, 199, 200).

[redacted]



Source: A) Clarity AD ((169)); B) Assuncao et al., 2022 (201)

Comparing the Clarity AD OLE data for lecanemab with a natural history of AD progression suggests there is an increasing treatment benefit with lecanemab beyond 18 months

During the Clarity AD OLE, the absolute treatment difference between lecanemab and a natural history cohort in CDR-SB continued to increase from 18 through to 36 months, with an absolute treatment difference of [redacted] at 18 months versus [redacted] at 36 months, illustrating cumulative benefit from lecanemab treatment compared to natural disease

progression (98). This cumulative benefit is a hallmark of treatments that delay disease trajectory.

The slowing of cognitive and functional decline seen on clinical scales translates into meaningful benefits on QoL measures

Progression of AD is associated with worsening QoL for patients. Maintaining QoL has been identified as a clinically meaningful benefit, with assessments providing unique perspectives from the patient and caregiver with respect to their own perceptions of the impact of the disease (202, 203). Complementing the robust primary and secondary outcomes, the QoL assessments in Clarity AD provide context and insights into both the disease impact, and the extent to which treatment can mitigate the loss of QoL even within an 18-month period. The primary and key secondary outcomes, along with these instruments, provide a comprehensive perspective on clinical meaningfulness.

In Clarity AD, lecanemab treatment was associated with a relative preservation of subject-reported QoL versus placebo. Consistent benefits were seen across different scales and within scales. At 18 months, the adjusted mean change from baseline in EQ-5D-5L and QOL-AD rated by the subject showed [redacted] less decline, respectively. For each QoL subject assessment, results separate in favour of lecanemab beginning at 6 months [redacted]

- In Clarity AD, lecanemab demonstrated a consistent effect across the domains/items relevant to AD within the QoL scales
- In the EQ-5D-5L (rated by the subject), the domains relevant to early AD - namely mood, self-care, and usual activities--favour lecanemab (mobility and pain or physical discomfort are not relevant symptomatology in early AD) (Appendix K.4.3.1)
- In the QOL-AD (rated by the subject), the benefit of lecanemab was evident on 11 of 13 items, ranging from less decline in functional abilities, to less decline in relationships, mood, finances, and life as a whole (Appendix K.4.3.2)

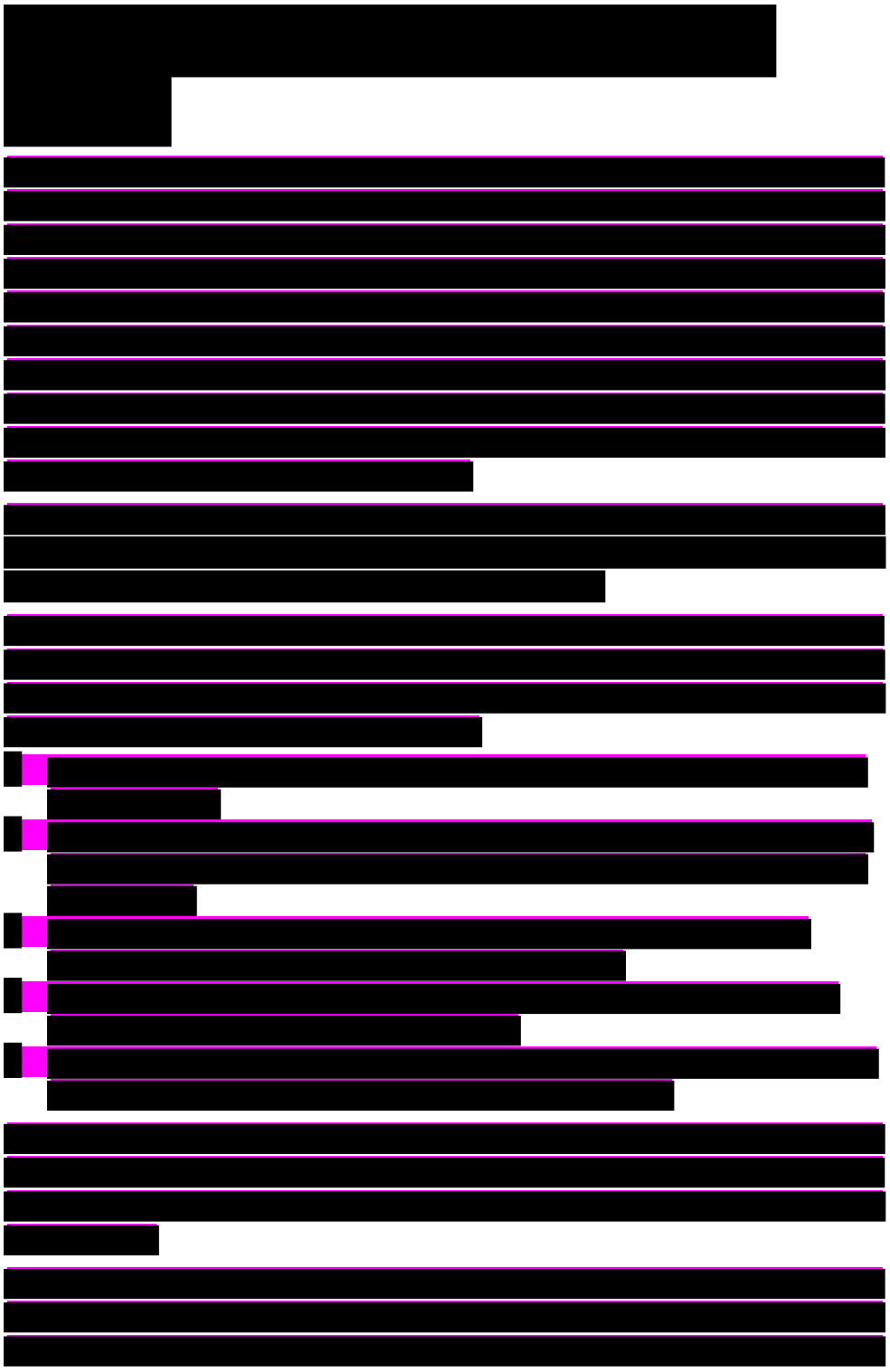
The slowing of patients' cognitive and functional decline also translates into meaningful benefits on the quality of life of caregivers

The progression of AD is distressing not only for patients, but also for their caregivers, and their families. The increased dependency of patients and emotional changes contribute significantly to caregiver burden, putting them at increased risk for physical morbidity and mental disorders (204).

In Clarity AD, caregiver burden, as measured by an adjusted mean change from baseline at 18 months using the ZBI, resulted in a [redacted] reduction in caregiver burden. Lecanemab benefit was seen across all 22 items of the ZBI, which includes caregiver-focused items, such as: not having enough time, enough money, enough privacy, feeling one's social life has suffered, feeling embarrassed by one's loved ones, and having lost control of one's life. All these items have been shown to be considered clinically meaningful to patients with AD and their caregivers (186).

In conclusion, maintaining patients within the earlier stages of AD where they can function more independently with better QoL, thereby delaying disability from AD, is highly meaningful to patients, caregivers, and treating clinicians. Lecanemab benefits patients and their caregivers by delaying the progression of AD, maintaining patients in earlier

disease states, in which they remain cognizant, functional, and capable of self-care, for longer.

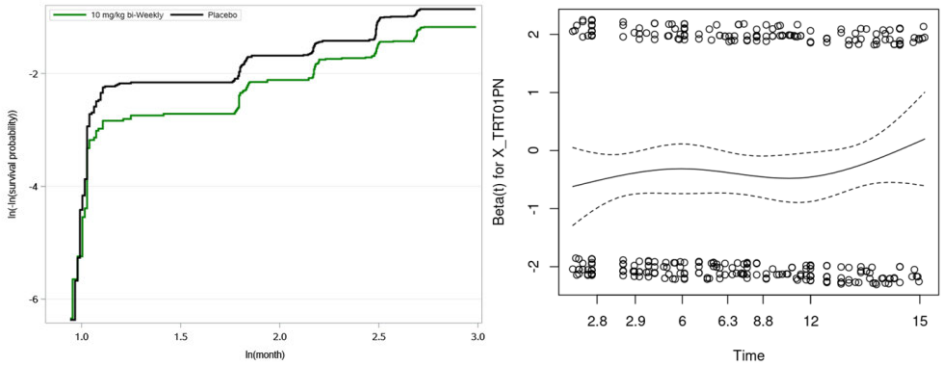


Appendix O. TTW – proportional hazards diagnostic

The proportional hazards assumption was assessed using log-cumulative hazards and Schoenfeld residuals plots for each analysis.

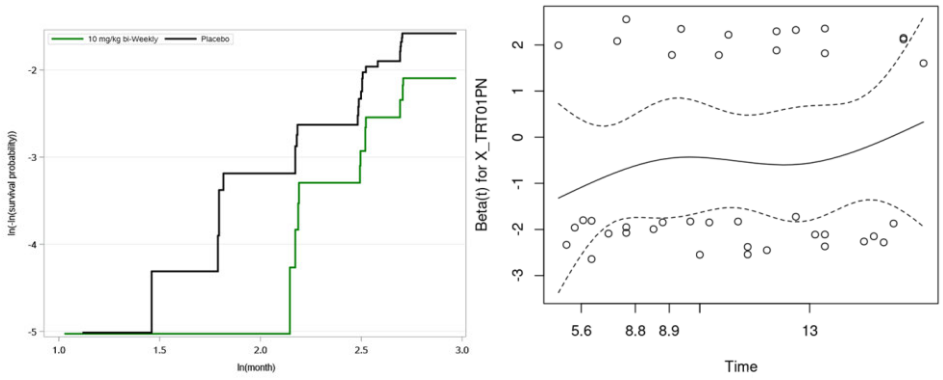
In the analysis of the [redacted] months data, the log-cumulative hazards are parallel following the start of the study and testing of the Schoenfeld residuals show no evidence that the proportional hazards assumption is violated (Figure 67, Figure 68 and Figure 69; [redacted] and [redacted] for the MCI due to AD, mild AD and combined populations, respectively). Based on these findings, the proportional hazards assumption holds and use of the semi-parametric Cox model to estimate the HRs for the stated transitions is appropriate.

Figure 67 Log-cumulative hazards and Schoenfeld residuals (MCI due to AD)



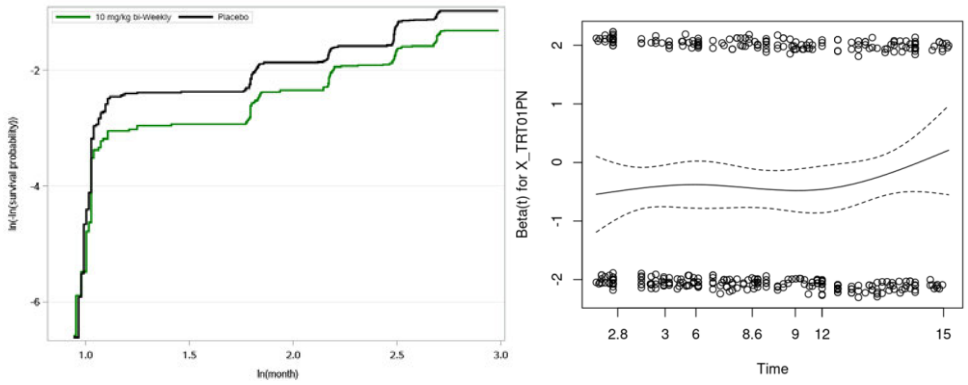
Abbreviations: AD= Alzheimer's disease; MCI = mild cognitive impairment

Figure 68 Log-cumulative hazards and Schoenfeld residuals (mild AD)



Abbreviations: AD= Alzheimer's disease

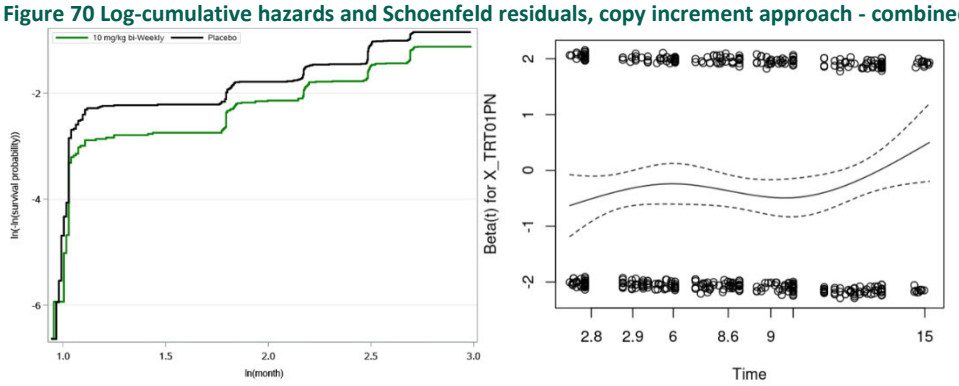
Figure 69 Log-cumulative hazards and Schoenfeld residuals, combined



Abbreviations: AD= Alzheimer's disease

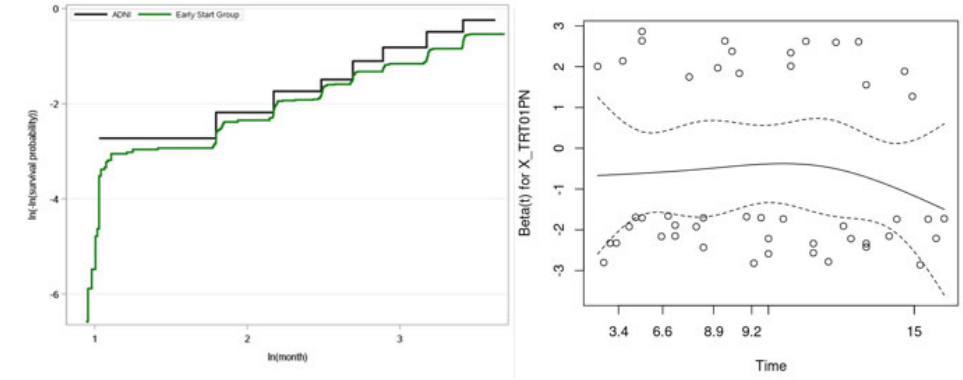
Similarly, the proportional hazards hold also when applying the copy increment approach, as shown in Figure 70 (Grambsch-Therneau test p value =0.095) and in Figure 71 data using the ADNI adjusted cohort.

Figure 70 Log-cumulative hazards and Schoenfeld residuals, copy increment approach - combined



Abbreviations: AD= Alzheimer's disease

Figure 71 Log-cumulative hazards and Schoenfeld residuals, 36 months data and ADNI adjusted cohort, combined



Abbreviations: ADNI= Alzheimer's Disease Neuroimaging Initiative

Appendix P. Health economic analysis inputs based on Global CDR

Table 125 Health state occupancy as defined by Global CDR at last assessment; Clarity AD (ITT FAS+, ApoE ε4 non-carriers and heterozygotes)

	MCI due to AD	Mild AD	Moderate AD	Severe AD
Lecanemab, n (%)				
ITT FAS+	[redacted]	[redacted]	[redacted]	[redacted]
MCI due to AD	[redacted]	[redacted]	[redacted]	[redacted]
Mild AD [redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Placebo, n (%)				
ITT FAS+	[redacted]	[redacted]	[redacted]	[redacted]
MCI due to AD [redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mild AD [redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: Clarity AD CSR (68)
Abbreviations: AD = Alzheimer's disease; CDR = Clinical dementia rating; FAS+ = full analysis set; ITT = Intent to treat; MCI = mild cognitive impairment
Note: ITT-FAS+ identifies randomized subjects who received at least 1 dose of study drug, and who had a baseline assessment and at least one post dose primary efficacy measurement.

Table 126 Summary of EQ-5D-3L utility index score in each health state using Global CDR score (ITT FAS+, UK tariff)

	Patients reported			By proxy		
	Lecanemab	Placebo	Combined	Lecanemab	Placebo	Combined

MCI due to AD	n	[redacted]
	Mean (C.I)	[redacted]
Mild AD	n	[redacted]
	Mean (C.I.)	[redacted]
Moderate AD	n	[redacted]
	Mean (C.I)	[redacted]
Severe AD	n	[redacted]
	Mean (C.I)	[redacted]

Abbreviations: AD, Alzheimer's Disease; FAS+, full analysis set; MCI, mild cognitive impairment; NA, not applicable; SD, standard deviation.

Table 127 Summary of the TTW – Global CDR analysis results

Data	HR (95% C.I.)
Combined health-states	[redacted]

Abbreviations: AD = Alzheimer's disease; C.I. = Confidence interval; TTW = Time to worsening

Table 128 Distribution of symptomatic treatment based on Global CDR health states

Data	Lecanemab and SoC arms
AChEI	
MCI due to AD	[redacted]
Mild AD	[redacted]
Moderate AD	[redacted]
Severe AD	[redacted]
Memantine	
MCI due to AD	[redacted]
Mild AD	[redacted]
Moderate AD	[redacted]
Severe AD	[redacted]

Abbreviations: AD = Alzheimer's disease

Appendix Q. Pattern of missing data per study arm

Table 129 Pattern of missing data and completion (Patient EQ-5D-Health today) by study arm

Time point	HRQoL population N	Missing N (%)	Expected to complete N	Completion N (%)
Lecanemab				
Baseline	[redacted]	[redacted]	[redacted]	[redacted]
6 months	[redacted]	[redacted]	[redacted]	[redacted]
12 months	[redacted]	[redacted]	[redacted]	[redacted]
18 months	[redacted]	[redacted]	[redacted]	[redacted]
Placebo				
Baseline	[redacted]	[redacted]	[redacted]	[redacted]
6 months	[redacted]	[redacted]	[redacted]	[redacted]
12 months	[redacted]	[redacted]	[redacted]	[redacted]
18 months	[redacted]	[redacted]	[redacted]	[redacted]

Source: CLARITY AD (68)

Abbreviations: EQ-5D-5L = European QoL – 5 Dimensions – 5 Levels; HRQoL = Health Related Quality of Life; N/A = Not available

Table 130 Pattern of missing data and completion (Patient by Study partner EQ-5D-Health today) by study arm

Time point	HRQoL population N	Missing N (%)	Expected to complete N	Completion N (%)
Lecanemab				
Baseline	[redacted]	[redacted]	[redacted]	[redacted]
6 months	[redacted]	[redacted]	[redacted]	[redacted]
12 months	[redacted]	[redacted]	[redacted]	[redacted]
18 months	[redacted]	[redacted]	[redacted]	[redacted]
Placebo				
Baseline	[redacted]	[redacted]	[redacted]	[redacted]
6 months	[redacted]	[redacted]	[redacted]	[redacted]
12 months	[redacted]	[redacted]	[redacted]	[redacted]
18 months	[redacted]	[redacted]	[redacted]	[redacted]

Source: CLARITY AD (68)

Abbreviations: EQ-5D-5L = European QoL – 5 Dimensions – 5 Levels; HRQoL = Health Related Quality of Life; N/A = Not available

Table 131 Pattern of missing data and completion (Study partner EQ-5D-Health Today) by study arm

Time point	HRQoL population N	Missing N (%)	Expected to complete N	Completion N (%)
Lecanemab				
Baseline	[redacted]	[redacted]	[redacted]	[redacted]
6 months	[redacted]	[redacted]	[redacted]	[redacted]
12 months	[redacted]	[redacted]	[redacted]	[redacted]
18 months	[redacted]	[redacted]	[redacted]	[redacted]
Placebo				
Baseline	[redacted]	[redacted]	[redacted]	[redacted]
6 months	[redacted]	[redacted]	[redacted]	[redacted]
12 months	[redacted]	[redacted]	[redacted]	[redacted]
18 months	[redacted]	[redacted]	[redacted]	[redacted]

Source: CLARITY AD (68)

Abbreviations: EQ-5D-5L = European QoL – 5 Dimensions – 5 Levels; HRQoL = Health Related Quality of Life; N/A = Not available

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