Medicinrådet

Bilag til Medicinrådets vurdering af donanemab til behandling af Alzheimers sygdom

Vers. 1.0

Bilagsoversigt

1. Ansøgers notat til Rådet vedr. donanemab til behandling af Alzheimers sygdom
2. Forhandlingsnotat fra Amgros vedr. donanemab til behandling af Alzheimers sygdom
3. Ansøgers endelige ansøgning vedr. donanemab til behandling af Alzheimers sygdom

Note to Medicinrådet regarding the assessment of donanemab in early symptomatic AD

Lilly appreciates the opportunity to comment on Medicinrådet's draft assessment of Kisunla® (donanemab) and the thorough work behind it. Lilly welcomes that Medicinrådet regards Alzheimer's disease as a serious, fatal brain disease with a high unmet need, and recognises the clinical meaningfulness of donanemab's efficacy: slowing the disease and reducing the risk of progressing to the next disease stage by 40.3% (CDR-G, HR 0.597) makes a real difference to patients. Lilly agrees with (a) the use of HR 0.62 in the main analysis, (b) the full treatment effect up to Month 18 for patients who stop after amyloid clearance at Month 6 or 12, and (c) the utility values from the lecanemab assessment, which have limited impact on the result (incremental QALY 0.17 with Landeiro et al. [1] versus 0.18). Lilly kindly asks Medicinrådet to keep the SmPC stopping rule in the main analysis (amyloid <24.1 CL), as it reflects real treatment duration and cost in Danish practice: the TB2 rule was a trial design criterion and is therefore more restrictive.

Beyond these points, Lilly would like to highlight three aspects that are particularly important for the Council's final decision:

1. Treatment effect beyond 18 months

A. The assumption is internally inconsistent. Medicinrådet accepts that patients who stop after 6 or 12 months keep their effect up to Month 18, i.e. for 12 or 6 months after the last dose (Figure 8 from the application; Jessen et al. 2026, supplementary Figure S2B [2]). Yet it assumes an abrupt loss of effect for patients treated for 18 months: a patient treated for 6 months keeps the effect for 12 months after the last dose, whereas a patient treated for 18 months keeps it for none. Medicinrådet considers it biologically plausible that a residual effect after treatment stop persist for a period and its own sensitivity analysis with effect up to 5 years after stopping lowers the ICER by 64%. An abrupt stop at Month 18 is difficult to reconcile with Medicinrådet's own assessment.

B. The data indicate that benefit persists.

- In the TB2 long-term extension (LTE) [3], the difference to the weighted ADNI cohort in early-start participants widened from −0.61 at Month 18 to −1.09 at Month 36 on CDR-SB (95% CI −1.76 to −0.41; Figure 9 in the application; Jessen et al. 2026, supplementary Figure S5A [2]). In participants who switched to placebo at Month 12 (n=171), the effect doubled between Month 18 and 36 (application, Figure 32).
- Amyloid re-accumulates slowly: an estimated 2.4 CL per year across four donanemab studies, so about 4.5 years from a mean of 12.7 CL to 24.1 CL. In participants who completed treatment by Week 24 or 52, mean amyloid stayed below 24.1 CL through Month 36 (application, Figure 37).
- Follow-up continues: about 200 participants have annual amyloid PET for 3 years, with completion expected in 2028.

Taken together, this is consistent with a disease-modifying mechanism: after plaque removal, continued dosing should not be required, as the benefit persists while amyloid slowly re-accumulates. Medicinrådet itself describes donanemab as disease-modifying. A symptomatic treatment would lose its difference when dosing stops, so removing the effect after 18 months models a symptomatic treatment, not a disease-modifying one.

C. Concerns raised by Medicinrådet

ADNI is a suitable external control. ADNI is a longitudinal cohort with a trial-like protocol, standardised eligibility criteria and scheduled assessments, set up to validate biomarkers for Alzheimer's disease trials [4]. Participants were selected to mirror TB2 (cognitively impaired, amyloid-positive, APOE4 non-homozygous) and weighted on key baseline characteristics, including CDR-SB. The weighted cohort followed the TB2 placebo arm closely over the first 18 months (Figure 36, application), which directly tests the control where placebo data exist. There is therefore limited reason to expect different progression thereafter. Medicinrådet notes slightly faster progression in the LTE phase than during the first 18 months. Slightly faster progression in the LTE phase is expected in AD where there is a non-linear progression. Over the same period, ADNI progressed faster than the donanemab group, so the difference to ADNI widened.

Why TB2 had no placebo group after Week 76. The 76-week placebo-controlled period followed the phase 2 trial TRAILBLAZER-ALZ, in which the primary endpoint (iADRS) was assessed at Week 76 and where donanemab separated from placebo from Week 36 (difference at Week 76: 3.20 points; 95% CI 0.12 to 6.27; P=0.04) [5].

Placebo control in TB2 was therefore justified until efficacy was established and 40 weeks more. Once TB2 had shown clinical benefit at Week 76 [6] in a serious, progressive disease, continued placebo would have meant an avoidable, irreversible loss of function when an effective treatment was available (Declaration of Helsinki [7]). Lilly understands the concern about using an external control, but a longer placebo-controlled period was not ethically possible. The design follows EMA's guideline (CPMP/EWP/553/95 Rev.2, sections 8.3.2 and 11.2) [8], which considers 18 months sufficient for confirmatory trials and recommends a delayed-start phase. Long placebo periods, as in EVOKE (semaglutide; 156 weeks; primary endpoint not met at Week 104) [9, 10], have been used where efficacy was unproven in previous randomized clinical trials before initiating phase 3. Lilly is not aware of any guideline requiring placebo control for more than 76 weeks, nor of an early symptomatic AD trial that continued placebo after efficacy was shown.

D. Lilly's ask. Sustained benefit over many years remains clinically plausible. NICE's External Assessment Group [11] modelled full effect for 2.5 years after treatment completion, followed by waning over 5 years, and Canada's CDA-AMC [12] modelled 3 years of full effect followed by waning over 7 years. These assessments thus allow a benefit to persist for up to 7.5 and 10 years after treatment completion, respectively, whereas Medicinrådet's main analysis assumes none after Month 18. Canada's expert committee (CDEC) concluded that the LTE suggests that the effect may persist beyond 18 months, while noting considerable uncertainty from the lack of a randomized comparator, the external control cohort and small effective sample sizes (draft recommendation [13], pp. 7–8). Like Medicinrådet, both assessments therefore see the uncertainty, but other HTA bodies handle it with gradual waning, not by assuming no effect after 18 months.
Lilly therefore respectfully asks Medicinrådet to review its main analysis and consider the evidence alongside the biological plausibility of waning over at least 5 years for patients completing treatment after 18 months.

2. NACC transition probabilities

The differences in mean baseline CDR-SB between NACC, ADNI (before weighting) and TB2 reflect the different purposes of each source, not unexplained variability. NACC was used to estimate transition probabilities for a model that follows patients through MCI, mild, moderate and severe AD, and death. Medicinrådet notes that NACC has more APOE4 homozygous patients than TB2 (13.5% versus 0%), which could overestimate progression, and that longer education in NACC may pull in the opposite direction. The evidence on homozygosity is also mixed: in ADNI and J-ADNI, cognitive decline in early AD did not differ between ε4 carriers and non-carriers or by the number of alleles [14], and Garcia et al. found no increased risk of faster progression with two copies [15]. The uncertainty is therefore two-sided, and the QALY gain is not clearly overestimated.

3. Amyloid and clinical outcome

Medicinrådet acknowledges a relationship between amyloid level and clinical change, but notes it is not proportional. Lilly agrees: amyloid is one of several drivers, including tau [16, 17], and Lilly uses it to support duration, not the size of the effect. Across six cohorts greater amyloid burden is associated with faster decline [16-21], and little progression is seen below about 50 CL [22, 23]. Lilly agrees with Medicinrådet that these cohorts are cognitively unimpaired people and show the natural relationship. In symptomatic AD, lower achieved amyloid is associated with slower decline, across individual TB2 participants and across anti-amyloid trials [24, 25]: those with the lowest post-treatment amyloid had a 76-week CDR-SB change of about +1.5 points, against +3 or more with higher residual amyloid (R^2 0.87) [25]. The clinical consequence of re-accumulation after plaque removal has not yet been observed, as anti-amyloid antibodies are the first treatments to remove plaque in symptomatic AD, and the direct evidence is now being built. Re-accumulation is slow (see section B.), while the clinical difference to ADNI kept growing for up to 36 months.

For patients with early symptomatic Alzheimer's disease and their families, a time-limited treatment that slows progression means more time in the earliest stages of the disease. Lilly would be grateful if the Council would weigh this benefit and the remaining uncertainties when considering the value of Kisunla® for Danish patients, and thanks Medicinrådet for the open dialogue.

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30.10.2026

LSC/IAS

Forhandlingsnotat

Dato for vurdering i Medicinrådet	25.11.2026
Leverandør	Eli Lilly
Lægemiddel	Kisunla (donanemab)
Ansøgt indikation	Behandling af voksne patienter med klinisk diagnosticeret let kognitiv svækkelse og let demens som følge af Alzheimers sygdom (tidlig symptomatisk Alzheimers sygdom), som er apolipoprotein E ε4 (ApoE ε4) heterozygote eller ikke-bærere, og som har bekræftet amyloid patologi
Nyt lægemiddel / indikationsudvidelse	Nyt lægemiddel

Prisinformation

Amgros har forhandlet følgende pris på Kisunla:

Tabel 1: Forhandlingsresultat

Lægemiddel	Styrke (pakning)	AIP (DKK)	Forhandlet SAIP (DKK)	Forhandlet rabat ift. AIP
Kisunla	350 mg (1 stk.)	5.664,65	[redacted]	[redacted]

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

Aftaleforhold

Amgros vil indgå en aftale på Kisunla ved en anbefaling i Medicinrådet. Aftalen gælder fra den 01.02.2027 til den 31.03.2029 med mulighed for at forlænge i 2x12 måneder. Leverandøren har mulighed for at sætte prisen ned i løbet af aftaleperioden.

Initiering af behandling med Kisunla skal ske gennem et centralt registreringssystem, der implementeres, som en del af et program for kontrolleret adgang, jf. EPAR for Kisunla. Et sådant registreringssystem vil forventeligt kræve vurdering i regionerne ift. det databeskyttelsesretlige, hvilket forventes at tage op til 2 måneder regnet fra anbefaling i Medicinrådet. Kan vurderingen ske på kortere tid vil Amgros melde dette ud. Patienter kan ikke opstartes i behandling før dette er vurderet i regionerne.

[redacted]

Informationer fra forhandlingen

[redacted]

Konkurrencesituationen

Kisunla er den anden potentielle behandlingsmulighed til Alzheimers i Danmark. Leqembi (lecanemab) til samme indikation blev vurderet i Medicinrådet i 2025, men er ikke anbefalet. Tabel 2 viser lægemiddeludgifter ved behandling med Kisunla for en behandlingsperiode på maksimalt 18 måneders.

Tabel 2: Lægemiddeludgifter pr. patient

Lægemiddel	Styrke (pakning)	Dosering*	Pris pr. pakning (SAIP, DKK)	Lægemiddeludgift pr. behandling (SAIP, DKK)**
Kisunla	350 mg (1 stk.)	Cyklus 1: 350 mg, i.v. Cyklus 2: 700 mg, i.v. Cyklus 3: 1.050 mg, i.v. Efterfølgende 1.400 mg, i.v., hver 4. uge	[redacted]	[redacted]

*Cykluslængde: 4 uger

** Behandlingslængde: 18 måneder

Status fra andre lande

Tabel 3: Status fra andre lande

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

Opsummering

Amgros vil indgå en aftale på Kisunla, hvis den anbefales af Medicinrådet. En aftale vil tidligst kunne træde i kraft når regionerne har haft mulighed for at vurdere det databeskyttelsesretlige i forbindelse med program for kontrolleret adgang på Kisunla.

Application for the assessment of Kisunla® (donanemab) for Mild Cognitive Impairment and Mild Dementia due to Alzheimer's Disease in adult patients that are apolipoprotein E ε4 (APOE ε4) heterozygotes or non-carriers

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

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Abbreviations

Abbreviation	*Definition*
AChE	Acetylcholinesterase
AChEI	Acetylcholinesterase inhibitor
AD	Alzheimer's disease
ADAS-Cog13	Alzheimer's Disease Assessment Scale – 13-item Cognitive subscale
ADCS-ADL	Alzheimer's Disease Cooperative Study – Activities of Daily Living
ADCS-iADL	Alzheimer's Disease Cooperative Study – instrumental Activities of Daily Living subscale
ADL	Activities of daily living
AE	Adverse event
amyloid-PET	Amyloid positron emission tomography
APOE	Apolipoprotein E gene
ARIA	Amyloid-related imaging abnormalities
ARIA-E	Amyloid-related imaging abnormality – oedema/effusion
ARIA-H	Amyloid-related imaging abnormality – microhaemorrhages and haemosiderin deposits
ATC-code	The Anatomical Therapeutic Chemical code
ATT	Amyloid-targeting therapy
Aβ	Amyloid beta
BL	Baseline
BSC	Best supportive care
CDR-G	Clinical Dementia Ratings Scale–Global Score
CDR-SB	Clinical Dementia Rating Scale – Sum of Boxes
CDSR	Cochrane Database of Systematic Reviews
CHO	Chinese Hamster Ovary
CI	Confidence interval
CIR	Copy increments in reference
CL	Centiloids
CNS	Central nervous system
CRP	C-reactive protein
CSF	Cerebrospinal fluid
CT	Computed tomography
DMT	Disease Modifying Therapy
DON	Donanemab
EMA	European Medicines Agency
EU	European Union
GFAP	Glial fibrillary acidic protein
GI	Gastrointestinal
GLMM	Generalised linear mixed model
HR	Hazard ratio
HRQoL	Health-related quality of life
HTA	Health Technology Assessment
iADL	Instrumental activities of daily living
iADRS	Integrated Alzheimer's Disease Rating Scale
ICER	Incremental cost-effectiveness ratio
IgG1	Immunoglobulin G1
IRR	Infusion-related reactions

IV	Intravenous
IVD	In vitro diagnostic
IWG	International Working Group
J2R	Jump to reference
KOL	Key opinion leader
LSM	Least squares mean
LTE	Long term extension
LYs	Life years
MCI	Mild cognitive impairment
mg	milligram
MMRM	Mixed models for repeated measures
MMSE	Mini-Mental State Examination
MoCA	Montreal Cognitive Assessment
MRI	Magnetic resonance imaging
MWPC	Meaningful within-patient change
N/A	Not applicable
N3pG Aβ	N-terminal truncated form of amyloid beta
NACC	National Alzheimer's Coordinating Center
NfL	Neurofilament light chain
NHS	England's National Health Service
NIA-AA	National Institute on Aging and Alzheimer's Association
NMDA	N-methyl-D-aspartate
NR	Not reported
PBO	Placebo
PC	Placebo-controlled
PET	Positron emission tomography
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PMRM	Progression model for repeated measures
Q4W	Every four weeks
QALYs	Quality-adjusted life years
QoL-AD	Quality of Life in Alzheimer's Disease questionnaire
SAEs	Serious adverse events
SD	Standard deviation
SE	Standard error
DKK	Danish krone
SLR	Systematic literature review
SmPC	Summary of product characteristics
SPECT	Single-photon emission computed tomography
SSRI	Selective serotonin reuptake inhibitors
SUVR	Standardised uptake value ratio
TB2	TRAILBLAZER-ALZ2
TB6	TRAILBLAZER-ALZ6
TE	Treatment-emergent.
TEAEs	Treatment-emergent adverse events
TTE	Time-to-event
TTO	Time trade-off
Tx	Treatment
USA	The United States of America
vMRI	Volumetric magnetic resonance imaging
W	Week

1. Regulatory information on the medicine

Overview of the medicine	
Proprietary name	Kisunla®
Generic name	Donanemab
Therapeutic indication as defined by EMA	Donanemab is indicated for the treatment of adult patients with a clinical diagnosis of mild cognitive impairment and mild dementia due to Alzheimer's disease, AD (early symptomatic AD) who are apolipoprotein E ε4 (ApoE ε4) heterozygotes or non-carriers with confirmed amyloid pathology.
Marketing authorization holder in Denmark	Eli Lilly Denmark A/S
ATC code	N06DX05
Combination therapy and/or co-medication	N/A
Date of EC approval	September 2025
Has the medicine received a conditional marketing authorization?	No
Accelerated assessment in the European Medicines Agency (EMA)	No
Orphan drug designation	No
Other therapeutic indications approved by EMA	No
Other indications that have been evaluated by the DMC	No
Joint Nordic assessment (JNHB)	Due to significant differences in healthcare organization, treatment practices, and available resources across countries, we do not expect Joint Nordic HTA Bodies collaboration to reduce the workload or time but rather increase the complexity of HTA.
Dispensing group	BEGR
Packaging – types, sizes/number of units and concentrations	Each Kisunla® vial contains 350 mg donanemab in 20 mL (strength: 17.5 mg/mL). Pack size: 1 vial.

2. Summary table

Summary	
Indication relevant for the assessment	Donanemab 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 symptomatic AD) who are apolipoprotein E ε4 heterozygotes (ApoE ε4) or non-carriers with confirmed amyloid pathology. There are no deviations from the European Medicines Agency (EMA) indication.
Dosage regiment and administration	The recommended dose of donanemab is 350 mg for the first dose, 700 mg for the second dose, 1050 mg for the third dose, followed by 1400 mg every 4 weeks. Treatment should be maintained until amyloid plaques are cleared as confirmed using a validated method. The maximum treatment duration is 18 months. To reduce burden, cost, and potentially unnecessary treatments, a response-guided, time-limited strategy is proposed, whereby treatment is completed at 12 months if amyloid plaque levels are reduced to minimal levels, as confirmed by an amyloid-PET scan (in line with the trial design).
Choice of comparator	No comparator, but addition to best supportive care (BSC), which consists of acetylcholinesterase (AChE) inhibitors and/or memantine. In the clinical documentation the comparator is described as placebo (i.e., BSC + placebo).
Prognosis with current treatment (comparator)	Dementia is the fourth leading cause of death in Denmark (1) and among older adults, represents the single greatest source of life years lost, surpassing other major conditions such as cancer and heart disease (2). As Alzheimer's disease progresses, patients experience worsening in cognitive, emotional, and physical function leading to functional disability and loss of independence, significantly affecting health-related quality of life both for patients and care partners (3). Currently, there is no cure for Alzheimer's disease and existing therapies provide temporary symptomatic relief without influencing the underlying disease pathology (4).
Type of evidence for the clinical evaluation	Randomized, placebo-controlled phase III(b) trials for efficacy (TRAILBLAZER-ALZ2, TB2 (5) and its long-term extension (6) and safety (TB2 and TRAILBLAZER-ALZ6, TB6 (7)). Data is provided for the subgroup of participants included in the EMA label. This entails data summarized in the summary of product characteristics (EU SmPC) as well as data where participants on contraindications in line with EMA label were

Summary	
	removed (EU eligible). The latter is presented to the extent possible and is used for the health economic assessment.
Most important efficacy endpoints (Difference/gain compared to comparator)	**Primary:** Change from baseline in the Integrated Alzheimer's Disease Rating Scale (iADRS) at Week 76: Donanemab demonstrated a 19.6% (95% CI 7.59, 31.69) slowing of disease progression versus placebo in the EU SmPC population and a 17.9% (95% CI 5.22, 30.58) slowing in the EU eligible population. **Secondary:** Change from baseline in the Clinical Dementia Ratings Scale – Sum of Boxes (CDR-SB) at Week 76: Donanemab showed a 28.5% (95% CI 17.44, 39.51) slowing of disease progression versus placebo in the EU SmPC population and a 28.2% (95% CI 15.18, 41.29) slowing in the EU eligible population. **Secondary (used in the health economic model):** CDR-SB risk of meaningful disease progression (Meaningful Within-Patient Change) from baseline to Week 76: In the EU SmPC population, donanemab reduced the risk of clinically meaningful worsening by 36.4% compared with placebo (HR 0.64; p<0.001); in the EU eligible population, the risk reduction was 38.0% (HR 0.62; p<0.001). **Other secondary/exploratory:** CDR-Global (CDR-G) risk of progression to a later clinical stage from baseline to Week 76: Donanemab reduced the risk of disease stage progression by 40.3% in the EU SmPC population (HR 0.60; p<0.0001) and by 47.2% in the EU eligible population (HR 0.53; p=0.0238) compared with placebo. Delay in CDR-SB disease progression at Week 76: In the EU SmPC population, 18 months of treatment with donanemab delayed disease progression by 5.82 months (95% CI 4.2, 7.44) versus placebo, corresponding to a 33.2% time saving (p<0.001). Proportion of participants achieving amyloid clearance (<24.1 Centiloids) after 12 months (Week 52), amyloid clearance was achieved in 69.5% (EU SmPC) and 69.7% (EU eligible) of donanemab-treated participants and at Week 76, in 80.8% and 80.5%, respectively (all p<0.0001 vs placebo). **Long-term extension – durability of clinical effect:** CDR-SB change from baseline versus weighted ADNI external control: In the EU SmPC population, donanemab showed a −0.57 difference at 18 months and −0.97 at 36 months compared with ADNI controls (p<0.001). Amyloid plaque levels following treatment completion: Mean amyloid levels remained below the clearance threshold through 36 months in participants completing donanemab

Summary	
	treatment by Week 52, with observed re-accumulation occurring at approximately 2.4 Centiloids/year.
Most important serious adverse events for the intervention and comparator	TB2: ≥1 SAE (n, %) was reported in the EU SmPC population in 127 (17.9%) of participants treated with donanemab vs 111 (15.2%) with placebo, and in the EU eligible population 89 (14.6%) vs 74 (12.3%), respectively (5). TB6 (EU eligible population, n=158): 14 (8.86%) experienced moderate or severe infusion-related reaction IRR and 37 (23.42%) experienced non-severe ARIA (Lilly Data on file). Key SAEs: ARIA events were the most important SAEs in both the EU SmPC and EU eligible population. Notably, the EMA label posology is based on TB6 (7) where the dose titration regimen reduced the relative risk of ARIA-E with 40.5% and showed a significant lower severity of ARIA-E (7).
Impact on health-related quality of life	Data on QoL-AD (a disease specific instrument) were collected in a subset of patients in TB2 (5). Given the 18 months trial duration data did not reflect the entire AD disease spectrum, and therefore HRQoL data used in this application is sourced from literature.
Type of economic analysis that is submitted	Cost-utility analysis (Markov model) and a budget impact analysis.
Data sources used to model the clinical effects	Efficacy: TB2 (NCT04437511), pivotal trial (5) and its long-term extension (6). Safety: TB6 (NCT05738486) (7)
Data sources used to model the health-related quality of life	Patient Health State Utilities: Landeiro et al. 2020 (8)
Life years gained	0.33 years
QALYs gained	0.61 QALY
Incremental costs	142,938.51 DKK
ICER (DKK/QALY)	232,912 DKK/QALY
Uncertainty associated with the ICER estimate	The most influential parameters are the HR vs comparator on CDR-SB scale (both for MCI due to AD and mild AD) as well as the RDI for donanemab.
Number of eligible patients in Denmark	[redacted]

Summary	
	[redacted].
Budget impact (in year 5)	[redacted]

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

3.1 The medical condition

Alzheimer's disease (AD) is a devastating, progressive neurodegenerative disorder. It is the most prevalent cause of dementia, accounting for approximately two-thirds of all cases (9, 10). The impact on public health is profound, as projections indicate dementia will become the third most common cause of death globally by 2040. In Denmark, dementia ranks as the fourth leading cause of death, with over 5,000 individuals dying from dementia in 2024 (11). Recognizing its seriousness, the United Nations formally acknowledged dementia in 2025 as a chronic disease requiring prioritization comparable to cancer and heart disease (12). Long before it proves fatal, dementia, including AD, follows a progressive course of cognitive and functional decline, ultimately leading to a complete loss of independence and imposing a substantial burden on the patient, care partner, healthcare system and society (13).

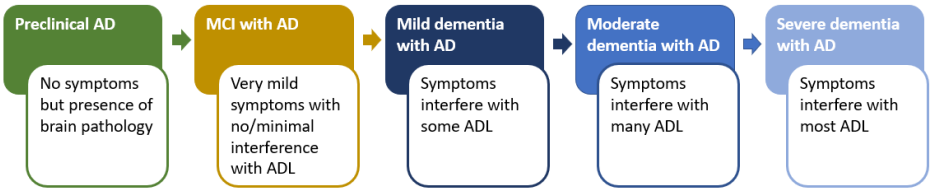
AD is characterized by distinct neuropathological changes in the brain, including extracellular accumulation of aggregated amyloid-beta (Aβ) plaques and intraneuronal neurofibrillary tau tangles. This accumulation of amyloid plaques is widely considered the initiating factor for AD pathogenesis, triggering a series of events that ultimately result in neuronal degeneration and cognitive decline (14, 15). This is also acknowledged among clinicians treating AD patients in Denmark (16, 17), and the National Knowledge Center for Dementia emphasizes that amyloid pathology is a first driver in the development of AD (18).

Clinical features of AD

Evidence indicate that the cognitive decline in AD progress continuously over a long period and that the neuropathological changes may begin more than 20 years before onset of clinical symptoms (19, 20). AD is thus regarded as a disease continuum commonly divided into four symptomatic stages of increasing severity: mild cognitive

impairment (MCI), mild, moderate, or severe dementia. The associated clinical features and symptom burden across the stages are illustrated in Figure 1 (19).

Figure 1. The AD continuum



Abbreviations: AD, Alzheimer's disease; ADL, activities of daily living; MCI, Mild cognitive impairment. Source: Adapted from (13)

Across this continuum, clinical features evolve from subtle cognitive and functional changes to severe impairment, underscoring the importance of accurate differentiation between disease stages for appropriate disease management.

MCI

Dementia specialists, including neurologists across Denmark, recognize MCI as a distinct phase within the AD spectrum (21). MCI is characterized by measurable cognitive deficits, such as difficulties with memory, language, and executive function, that do not yet substantially interfere with basic daily functioning or overall independence. Individuals with MCI may begin to struggle with complex tasks like managing finances, shopping, or cooking, but are generally still capable of handling basic daily activities (19, 22, 23). This stage often involves subtle errors and decreased efficiency, but patients retain much of their autonomy.

Mild AD

As the disease progresses to mild AD, the clinical presentation becomes more pronounced. Mild AD is characterized by impairment in at least one cognitive domain, most commonly memory, but also language or visuospatial skills and clear evidence of reduced ability to perform activities of daily living. At this stage, patients experience a noticeable loss of independence, requiring support with everyday activities and often struggle with communication and problem-solving (24).

Moderate and severe AD

In the later stages of AD (moderate and severe) the seriousness of the disease becomes increasingly evident. Moderate AD is characterized by further deterioration in cognitive abilities, including profound deficits in memory, language, visuospatial orientation, and executive functions. Patients frequently lose track of time and place, become disoriented, and require assistance with basic activities such as dressing, bathing, and eating. Communication becomes significantly impaired, and behavioral symptoms like agitation, aggression, and mood disturbances may arise (13, 25). Severe AD represents the most advanced stage, where mental functioning and physical abilities are profoundly compromised. At this point, patients often lose the ability to communicate, recognize loved ones, or perform any daily activities independently (13, 25). Movement and motor skills deteriorate, leading to immobility, increased risk of infections, and ultimately, they need constant care.

Progression through these stages highlights the devastating impact of AD, culminating in a complete loss of independence placing a considerable burden on families and the healthcare system. Thus, understanding the trajectory of AD is important to provide appropriate care and planning support, which reinforces a need for timely diagnosis and intervention (26-28).

Diagnosis

In primary care, patients with suspected AD will undergo a basic diagnostic assessment. If cognitive impairment or dementia is suspected, patients are referred to a hospital-based memory clinic for further evaluation. The diagnostic work-up is based on a combination of clinical history, information from a close relative, objective cognitive assessment, and evaluation of functional abilities. The assessment may include (29-32):

- Structured anamnestic interview with the patient and close relatives
- Clinical examination
- Cognitive and functional assessment, using validated instruments; Mini-Mental State Examination (MMSE), or with Addenbrooke's Cognitive Examination (ACE) (33)
- Laboratory tests (blood, ECG) to exclude other reasons
- Structural brain scan (CT or MRI) to exclude other reasons
- Neuropsychological testing, when required

In selected cases, supplementary investigations may be performed to support the diagnostic evaluation, particularly where the diagnosis is uncertain or to assess underlying pathology. These may include:

- Cerebrospinal fluid (CSF) analysis for AD biomarkers (Aβ1-42, total-tau, p-tau or the ratio between Aβ42/p-tau to confirm AD)
- Functional imaging (e.g. PET-FDG, SPECT-CBF scan, DAT-SPECT)
- Amyloid PET imaging (e.g. PiB-PET)
- Electroencephalography (EEG)
- Genetic testing, in rare and selected cases

A Danish clinician states that amyloid PiB-PET is generally offered when lumbar puncture is contraindicated (34). In addition, many patients who undergo MRI have also had either FDG-PET imaging or CSF biomarker test. At the end of the assessment, all patients are given a syndromic diagnosis based on clinical criteria: normal cognition, mild cognitive impairment, or dementia (31).

Burden of the disease

Dementia primarily affects individuals over the age of 65 but can occur as early as age 40 to 50 (26). According to a Danish national registry-based cohort study, individuals diagnosed with dementia can lose up to 10 years of life expectancy following a dementia diagnosis, with particularly elevated mortality rate ratios and substantial life years lost (LYL) observed in the younger segment of the cohort (beginning at age 65). Dementia was identified as the leading cause of death associated with the greatest LYL, surpassing other major conditions such as cancer and heart disease (2). Dementia due to AD often occurs alongside other health conditions, which can worsen overall survival. According to

a Swedish study, lower cognitive function is associated with an increased risk of cause-specific mortality. This suggests that slowing AD progression could reduce mortality across all causes (35).

The humanistic burden of AD, with the impact on both patients and care partners, is considerable already in the early stages of AD (3, 36). In the What Matters Most study, 25% and 50% of people with MCI and mild dementia due to AD reported finding daily tasks more difficult (36). Moreover, studies have demonstrated that Heath-Related Quality of Life (HRQoL), as rated by both patients and care partners is reduced even in individuals with early symptomatic AD with increasing deficits following disease severity (37). Other factors have consistently been found to influence HRQoL in individuals with early AD. For instance, a meta-analysis (37) indicated that depression, anxiety, and neuropsychiatric symptoms are linked to poorer HRQoL, while elements such as relationships, social engagement, and functional ability contribute to higher HRQoL.

Measuring HRQoL in individuals with AD is however complex. Numerous factors influence this construct and capturing accurate information from patients can be challenging (37). Even early in the disease course, patients may experience decreased insight, which limits their ability to fully understand the impact of their disease on daily functioning. This can result in over-optimism regarding their own HRQoL (8, 38). Measuring HRQoL through care partner reported outcomes may thus be seen as appropriate.

As AD severity increases, so does the burden on care partners as measured by the increase in time spent on activities of daily living (ADLs) (39-41). In Denmark, relatives often take on the responsibility of providing care at home (11). An independent national publication by Danish Patients shows that almost half of the Danish population are relatives of a person with illness or disability, and most will take on this role at some point in their lives. It is anticipated that nearly half of all care partners (48%) who provide help to older adults do so for someone with AD or another dementia (42). Relatives provide a wide range of support, including motivation, practical assistance and coordination with public services, with one in four spending 4 to 9 hours per week in this role, and around one in three reporting consequences for their work or education (43). This is supported by a study in a Swedish population, showing that informally the care partner dedicated more than three hours per day, totaling 103 hours per month, caring for the AD patient (44). Care partners of individuals with AD thus experience higher levels of stress, depression, and reduced quality of life, with the burden intensifying as the disease progresses (45).

In Denmark, the direct healthcare and social costs associated with dementia are estimated to be around DKK 10 billion annually. Additionally, indirect costs, such as the loss of earnings for relatives, are estimated to be just under DKK 7.4 billion. Furthermore, extra costs should be added as the extra expenses for treatment by the patient's general practitioner and hospital visits, as well as the increased health issues among relatives. Consequently, dementia poses a significant challenge for both the healthcare system and society, a challenge that is expected to intensify with the growing number of people affected by the condition (46-48).

3.2 Patient population

A global study estimates the prevalence of MCI due to AD at 8.4%, and mild AD at 2.2%, among individuals aged 60 and older (49). With approx. 1.65 million people in this age group in Denmark, these prevalence numbers correspond to about 140,000 and 36,000 individuals, respectively (50). However, these figures are theoretical, as most individuals are not currently diagnosed. According to the National Dementia Research Centre, about 40,000 people were registered with dementia in Denmark in 2024, with 8,000-9,700 new registrations each year (51). These numbers include all stages and etiologies; after adjusting for the proportions with mild-stage dementia and AD etiology, the numbers become significantly smaller (Table 1). Note that these do not include individuals with MCI who are even more scarcely registered, with about 2,000 in the Danish quality database for Dementia (DanDem) annual report 2024, of which roughly half have AD (52).

Table 1 Incidence and prevalence of mild AD in the past 5 years

Year	2020	2021	2022	2023	2024
Incidence in Denmark*	2,186	2,173	2,293	2,579	2,333
Prevalence in Denmark*	10,384	10,411	10,304	10,317	10,737

*Estimates of registered mild AD, based on "Forekomst af demens i Danmark | Nationalt Videnscenter for Demens" (51), adjusted for 62% with underlying AD etiology (10) and 43% with mild AD according to DanDem annual report 2024 (52). NB. These data only include patients with a diagnosis and excludes patients with MCI.

Table 2 presents the patient funnel in line with a previous DMC assessment of another amyloid-targeting therapy (53).

Table 2 Patient funnel estimates

Estimates of eligible treatment population		Note
Patient base	2,490	Number of patients with Alzheimer's
10% in anticoagulation therapy	-249	
15% have contraindications to MRI scanning	-373	DMC estimates that 15% have contraindications to MRI scanning.
Correction for double counting	+37	It is assumed that there is an overlap between the two above groups.
Patients who already have an MRI scan today	-446	DMC estimates that 20% and 25% of patients with MCI and mild AD have a valid MRI scan.
Unscanned patient base	1,459	
50% do not want treatment	-952	Assumption that 50% do not want treatment with donanemab.
Patients for MRI scanning regarding donanemab suitability	729	Estimated number of MRI scans performed for diagnostics

20% due to contraindications found during MRI scanning	-190	DMC estimates that 20% of MRI scans show contraindications for donanemab
Potential candidates for ApoE4 testing	762	Estimated number of ApoE4 tests based on lumbar puncture results
15% of tests show ApoE4 homozygotes	-144	ApoE4 homozygotes are not candidates
Patients eligible for the treatment with donanemab	648	Calculated from above assumptions

Abbreviations: AD, Alzheimer's disease; APoE4, Apolipoprotein E gene; DMC, Danish Medicines Council; MCI, Mild cognitive impairment; MRI, Magnetic Resonance Imaging.

Estimates of eligible patients in 2024 (Table 2) were thus used to make a projection of the eligible treatment population from 2026 to 2030 (Table 3). A gradual uptake among eligible patients is expected during the first 2 years following the introduction of donanemab. The approach assumes that a selected number of designated specialty centers, referred to as "Centers of Excellence" (see Section 3.4.2), will initially administer donanemab, recognizing that donanemab is a novel treatment with administration and monitoring requirements that differ from those of treatments currently used in memory clinics, requiring a period of clinical adaptation.

[redacted] It is assumed that patients treated with donanemab undergo a PET scan at 12 months with approx. 70% completing treatment due to amyloid clearance (54). Therefore, the estimated number of patients treated every year considering gradual uptake and amyloid clearance completion is a cumulative number, summing up the new patients entering treatment every year with the rest of the patients remaining on treatment for the maximum of 18 months. See also Section 13 budget impact analysis.

Table 3 Estimated number of patients eligible for treatment

Year	2026	2027	2028	2029	2030
Number of patients eligible for treatment with donanemab in the coming years (per year)	650	650	650	650	650
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Estimated number of patients treated every year considering a gradual uptake and amyloid clearance completion* (cumulative)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

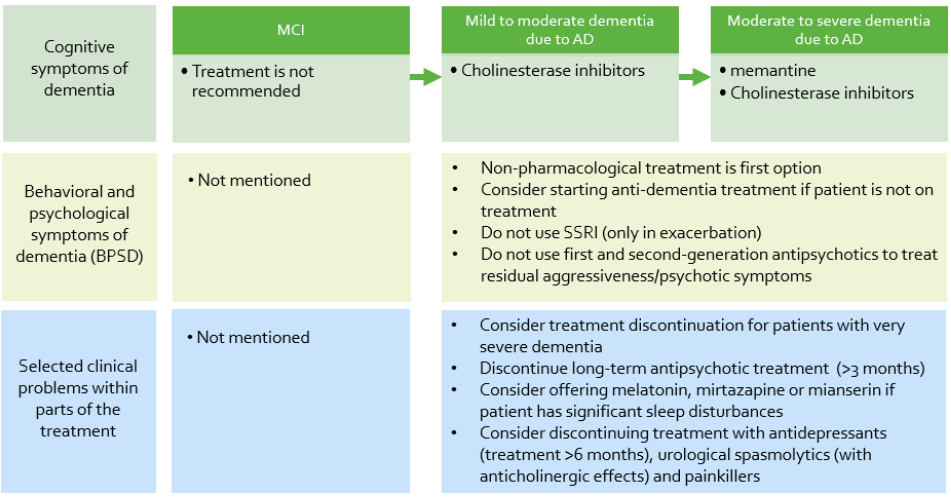
*Patients undergo an amyloid-PET scan at 12 months and 69.7% complete treatment given amyloid plaque clearance (<24.1 Centiloids per SmPC stopping rule). Source: Eli Lilly, Data on file.

3.3 Current treatment options

National and international pharmacological treatment guidelines exist for the management of AD, but these have not been updated in recent years reflecting a lack of approved new treatment options (55-58). There is no cure for AD, and current treatments provide only symptomatic relief without modifying the underlying disease process or slowing progression (4, 58).

In Denmark, several national clinical guidelines relevant to dementia and its treatment exist. These guidelines are currently considered outdated by Sundhedsstyrelsen but are still presented here due to the lack of an updated version. In these guidelines, treatment recommendations are divided according to stage of AD (summarized in Figure 2). The first stage is MCI, where the patient presents with a mild cognitive impairment but the diagnostic criteria for dementia is not yet met. Following MCI, AD dementia is divided into two stages: mild to moderate and moderate to severe.

Figure 2 Danish treatment guidelines for Alzheimer's Disease dementia



Abbreviations: AD, Alzheimer's disease; BPSD, behavioral and psychological symptoms of dementia; MCI, mild cognitive impairment; SSRI, Selective serotonin reuptake inhibitors. Source: (30, 59-63)

The national clinical guideline for investigation and treatment of dementia, published in 2013, provides recommendations for managing cognitive symptoms. There is no approved treatment for cognitive symptoms for people with MCI. The recommended treatment for cognitive symptoms for mild to moderate AD is a cholinesterase inhibitor and for moderate to severe AD is memantine. However, in current clinical practice, cholinesterase inhibitors are often used alongside memantine to relieve cognitive symptoms of moderate to severe AD (63, 64).

The national clinical guideline on the prevention and treatment of behavioral and psychological symptoms in people with dementia have been updated in 2025. The recommendations focus on the behavioral and psychological symptoms of dementia. No treatment recommendation could be identified for MCI. Recommendations include: using structured interventions to promote activity and relationships; improving physical environment (e.g., interior design, lighting, wall colors); and avoiding antipsychotics for behavioral symptoms due to serious side effects and lack of proven benefit, except for short-term use in severe cases (65).

Finally, the national clinical guideline for dementia and medicines, published in 2018 and currently being updated, presents several recommendations to selected clinical problems identified in some parts of the treatment of dementia patients (not specific to AD). Treatment should be stopped for very severe dementia. Long-term use of antipsychotics, antidepressants, urological spasmolytics, and painkillers is not advised. Sleep disturbances may be treated with melatonin, mirtazapine, or mianserin.

Unmet medical need

Existing treatment options for AD have included non-pharmacological and symptomatic treatments. Symptomatic treatments do, however, not alter the disease course. As already described, when a patient becomes cognitively and functionally more impaired, both patient and care partner quality of life decreases and care burden increase (66, 67). There is thus an urgent need for therapies that slow progression in early AD and have the potential to enable patients to retain their independence and HRQoL for longer.

Since there have been few advances in the treatment of AD since the symptomatic AChEI were approved 20 years ago, the need remains high for early and effective treatment options. With respect to new treatments, AD has one of the highest research and development failure rates. Between 1998 and 2017, 146 drugs for the treatment of AD were tested in clinical trials and rejected, with only four making it through the approval process (donepezil, rivastigmine, galantamine, and memantine) (68). Despite decades of extensive research that initially did not translate into approved therapies (aducanumab, bapineuzumab, crenezumab, gantenerumab and solanezumab), incremental advancements in clinical trial design, diagnostics, patient selection, and therapeutic strategies. This ongoing refinement has culminated in recent breakthroughs in the management of AD (5, 69). This is acknowledged by clinical experts, including a Danish AD researcher, who emphasizes the need to distinguish earlier amyloid-targeting trials from more recent studies considering the substantial methodological heterogeneity within AD research. Consequently, meaningful conclusions regarding efficacy cannot be drawn by pooling results across all products in development, as attempted in a recent Cochrane analysis (70). Thus, the value of clinical experience cannot be overstated, as it continues to propel progress in understanding the disease mechanisms. Similar to the transformative outcomes seen in cancer research, where continuing steps forward has ultimately led to cures, these advances in AD illustrate the importance of sustained commitment to innovation (68, 71).

3.4 The intervention

Donanemab is an immunoglobulin gamma 1 (IgG1) monoclonal antibody with high affinity for a modified, N terminal truncated form of amyloid beta (N3pE Aβ). N3pE Aβ is present in brain amyloid plaques at low levels and not detected in plasma and CSF. Donanemab binds to N3pE Aβ and aids plaque removal through microglial-mediated phagocytosis. A summary of the product characteristics is presented in Table 4.

Table 4 Characteristics of Kisunla® (donanemab)

Overview of intervention	
Indication relevant for the assessment	Donanemab is indicated for the treatment of adult patients with a clinical diagnosis of mild cognitive impairment and mild dementia due to AD (Early symptomatic AD) who are apolipoprotein E ε4 (ApoE ε4) heterozygotes or non-carriers with confirmed amyloid pathology.
ATMP	N/A
Method of administration	Donanemab is for intravenous (IV) use. Each vial is for single use only. Diluted solution should be administered over a period of at least 30 min.
Dosing	Donanemab should be administered every 4 weeks. The recommended dose of donanemab is 350 mg for the first dose, 700 mg for the second dose, 1050 mg for the third dose, followed by 1400 mg every 4 weeks up to a maximum of 18 months.
Dosing in the health economic model (including relative dose intensity)	The dosing recommended in the SmPC is used in the health economic model. The relative dose intensity (RDI) used in the model is 97.28%*.
Should the medicine be administered with other medicines?	No.
Treatment duration / criteria for end of treatment	Treatment should be maintained until amyloid plaques are cleared as confirmed using a validated method. The maximum treatment duration is 18 months, which should not be exceeded even if plaque clearance is not confirmed. This application proposes a response-guided, time-limited strategy, whereby treatment is completed upon confirmation of amyloid plaque clearance. In line with the TB2 clinical trial design, an amyloid-PET scan at 12 months can be used to evaluate amyloid clearance. Clearance in the SmPC was defined as a reduction in amyloid plaque to less than 24.1 Centiloids (CL), consistent with a negative visual read on a PET scan. If cleared patients can complete treatment at this time point according to the SmPC. Currently, amyloid-PET confirms amyloid plaque clearance in clinical practice in Denmark. Emerging blood-based biomarkers, if validated for this purpose, could offer a complementary approach and help reduce demand on PET infrastructure (72). The benefit-risk of treatment should be reassessed at regular intervals on an individual basis and considering the rate of disease progression. Consideration should be given to

Overview of intervention	
	discontinuing treatment before the end of 18 months, if patients progress to moderate AD.
Necessary monitoring, both during administration and during the treatment period	Treatment should be initiated by a physician experienced in the diagnosis and treatment of AD with timely access to MRI and preferably amyloid-PET. Donanemab should be administered under the supervision of a multidisciplinary team trained in detection, monitoring and management of ARIA and experienced in detecting and managing infusion-related reaction (IRR). Patients should be observed post-infusion for a minimum of 30 min.
Need for diagnostics or other tests (e.g. companion diagnostics). How are these included in the model?	A recent (within 6 months) brain MRI should be available prior to initiating treatment with donanemab to evaluate for pre-existing ARIA. An MRI should be performed prior to the second dose (at 1 month), prior to the third dose (at 2 months), prior to the fourth dose (at 3 months), and prior to the seventh dose (at 6 months). In patients with ARIA risk factors such as APOEε4 heterozygotes, and/or patients with previous ARIA events earlier in treatment, an MRI at one year of treatment (prior to the twelfth dose) should as well be performed. If a patient experiences symptoms suggestive of ARIA at any time during treatment, clinical evaluation should be performed including an MRI. APOEε4 genotype should be assessed by a CE-marked in vitro diagnostic (IVD) with the corresponding intended purpose. If the CE-marked IVD is not available, an alternative validated test should be used. Aβ evidence consistent with AD should be confirmed using a validated test (e.g. PET scan, CSF, or another appropriate test). Within few years, validated blood-based biomarkers may offer an alternative and help free up test resources and save costs (27). It is also proposed to use an amyloid-PET to confirm amyloid plague clearance after 12 months treatment. The model provides the option to include costs associated with diagnostic testing, amyloid detection in line with the stopping rule in the SmPC and monitoring costs for ARIA events (see details in Section 11).
Package size(s)	Each Kisunla® vial contains 350 mg donanemab in 20 mL (strength: 17.5 mg/mL). Pack size: 1 vial.

Abbreviations: AD, Alzheimer's disease; EMA, European Medicines Agency; IV, intravenous; MCI, mild cognitive impairment; MRI, magnetic resonance imaging; Q4W, every four weeks. Source: (73)

*In the model, the relative dose intensity (RDI) for donanemab was adjusted to account for a proportion of patients for whom treatment was interrupted due to non-severe ARIA cases, with duration of treatment interruption as observed in the EU eligible patient population from the TB6 trial. The RDI is intended to represent the ratio between the dose effectively administered and the target dose. An overall RDI of 97.28% was applied for donanemab, calculated as a weighted average based on the following inputs: the proportion of patients for whom treatment was interrupted due to ARIA (23.42%)(74), the mean duration of treatment

interruption as observed from the TRAILBLAZEER-ALZ6 trial (61.9 days)(75), and the trial duration (equivalent to 19x28-day dosing cycles), informed by the European Product Monograph of Donanemab (76).

3.4.1 Description of ATMP

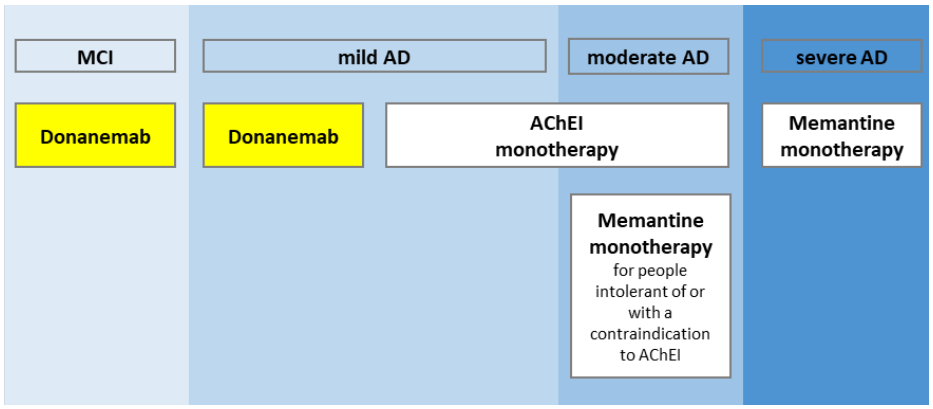
Not applicable.

3.4.2 The intervention in relation to Danish clinical practice

Donanemab should be considered a treatment choice for slowing progression of AD in adult patients with a clinical diagnosis of MCI or mild dementia due to AD who are apolipoprotein Eε4 (ApoEε4) heterozygotes or non-carriers with confirmed presence of amyloid pathology. Contraindications include ApoEε4 homozygotes, patients with baseline superficial siderosis, poorly controlled blood pressure defined as systolic blood pressure ≥140mmHg and diastolic blood pressure ≥90mmHG and anticoagulant use.

Due to the current lack of pharmacological treatment options for MCI, an MCI due to AD treatment pathway has yet to be established. However, a discussion paper from National Health Service (NHS) England 'Dementia programme and preparation for new Alzheimer's disease modifying treatments'24 (last updated 1 February 2024) includes a diagram showing the likely position of new medicines for AD which accords with the company's proposed positioning of donanemab, shown in Figure 3 (77).

Figure 3 First-line therapies for mild cognitive impairment and Alzheimer's disease at different severity levels



[a] For people with an established diagnosis of AD who have moderate or severe disease and who are already in receipt of AChEI therapy can be offered memantine in addition to the AChEI.

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

Source: Figure based partly on a diagram presented in Annex A of the NHS England discussion paper 'Dementia programme and preparation for new Alzheimer's disease modifying treatments'24 (77)

As Danish guidelines do not recommend any treatment for MCI, donanemab is expected to be the first treatment approved for this subpopulation. The recommended treatment for cognitive symptoms for mild and moderate AD mostly consists of a cholinesterase inhibitor (alternatively memantine) that do not alter the disease progression. Hence, for patients with mild AD, donanemab is expected to be an additional treatment that can be used in combination with the available symptomatic treatment options (in accordance with EMA approved indication).

A distinguishing benefit of donanemab is the potential to complete treatment once amyloid plaque is cleared from the brain. In TB2, amyloid-PET scans were conducted at 6 and 12 months to assess plaque clearance, after which 294 participants had completed treatment and switched to placebo. Trial data showed that participants who completed treatment following amyloid clearance experienced clinical benefits comparable to participants who continued treatment for the maximum duration of 18 months (see more details in Figure 8 in Section 6.1.4). This benefit was also observed during a long-term extension study, in which donanemab treatment demonstrated growing effect sizes up to 36 months (see more details in Figure 9 in Section 6.1.4).

Such a response-guided, time-limited strategy with donanemab could reduce cumulative drug exposure while maintaining sustained clinical benefit. This approach may mitigate long-term treatment-related risks, reduce patient and care partner burden, and provide a predictable and manageable treatment pathway for memory clinics, while supporting efficient use of healthcare resources. This approach is endorsed by both neurologists and a nuclear medicine specialist (14, 15),(34, 78). In particular, the nuclear medicine specialist considers a response-guided, time-limited strategy to be clinically sound and feasible within the Danish healthcare system. The use of objective imaging to confirm treatment response and guide completion aligns with established practice from oncology, such as lymphoma and brain tumors, where imaging-based response assessment is routinely used to avoid continued treatment without demonstrated benefit. Similarly, donanemab treatment can be completed, however, with a positive stopping rule.

Moreover, PET capacity is expected to be sufficient under a phased introduction. Denmark has extensive PET infrastructure, and most hospitals already have access to PET scanning either locally or through established regional collaboration, with existing scanners often underutilized (79). Radiotracers can be produced centrally or locally, and current waiting times are considered compatible with a PET-based response assessment after for example 12 months of treatment. Response-guided treatment is viewed as ethically appropriate and consistent with existing clinical standards. Overall, the nuclear medicine specialist supports a pathway using PET for response assessment as clinically meaningful, implementable, and supportive of efficient use of healthcare resources (78). Treatment with donanemab also requires MRI monitoring for ARIA. According to Eurostat, approx. 552,000 MRI scans are currently performed per year in Denmark. The expected additional need for MRI scans due to donanemab treatment in clinical practice is estimated at approx. 3,250 scans annually (for 650 patients) at the national level, corresponding to about 0.6% of total annual MRI activity. The estimated increase in activity is therefore considered to be of limited magnitude and is overall expected to be manageable within existing MRI capacity, primarily through planning and efficient use of current resources. Any potential regional or local variation is not expected to alter this overall assessment (79).

It is thus anticipated, that a response-guided, time-limited strategy using amyloid-PET confirmation should be feasible if initially selecting hospitals designated as “Centers of Excellence”, with access to MRI, infusion facilities, AD specialists, multidisciplinary teams and access to amyloid-PET (80-82). Neurology clinics across the Country have already

been mentioned in “Sundhedsstyrelsen Specialeplan for Neurologi, 2025” to handle complex treatments within neurology (83).

3.5 Choice of comparator(s)

Concomitant symptomatic, standard-of-care AD medications were permitted (i.e. AChE inhibitors and/or memantine), in the TB2 trial (pivotal trial). These treatments will hereafter be designated as best supportive care (BSC) (details provided in Appendix K). Dosing was required to be stable for approx. ≥30 days prior to randomization. In TB2, approx. 60% of participants in each treatment group received BSC at baseline (5).

The relevant comparator is thus composed of no addition to BSC (details are provided in Appendix K). This has been validated with a clinical expert with experience in treating AD in Danish clinical practice (34). In the clinical efficacy chapters, the comparator to donanemab is described as placebo (i.e., BSC + placebo).The information for BSC is presented in Table 88 in Appendix K.

Table 5 Characteristics of comparator

Overview of comparator
Not applicable. See Table 88 in Appendix K.

3.6 Cost-effectiveness of the comparator(s)

The comparator is no addition to BSC, corresponding to placebo and described in the clinical efficacy section (TB2). No DMC assessment was identified for the BSC treatments, i.e. acetylcholinesterase inhibitors (donepezil, galantamine, rivastigmine) and memantine (details are provided in Appendix K). These treatments are considered established standard treatments in Danish clinical practice in AD. The costs for BSC were considered low.

3.7 Relevant efficacy outcomes

3.7.1 Definition of relevant efficacy outcomes

According to EMA’s scientific guideline, for patients with established AD dementia, efficacy should be assessed in the following domains: cognition, as measured by objective tests (cognitive endpoint); (instrumental) activities of daily living (functional endpoint); and overall clinical response, as reflected by global assessment (global endpoint) (84). Two key assessment tools have been validated for this purpose (85).

The first tool is the integrated Alzheimer’s Disease Rating Scale (iADRS), which offers a sensitive measure of the impact of cognitive decline on daily functioning. iADRS achieves this by combining two well-established scales: the Alzheimer’s Disease Assessment Scale-

Cognitive subscale (ADAS-Cog13) and the Alzheimer's Disease Cooperative Study – Instrumental Activities of Daily Living (ADCS-iADL) (86).

The second tool being the Clinical Dementia Rating Scale – Sum of Boxes (CDR-SB), a clinician-reported outcome measure designed to stage disease severity. CDR-SB uses a semi-structured interview with patients and informants, enabling clinicians to rate symptoms across six distinct domains of cognition and function, thus providing a comprehensive view of how cognitive decline affects everyday activities (87). The EMA guideline requires efficacy in both cognitive and functional domains and recognizes CDR-SB as appropriate primary endpoints for early AD.

The primary objective of TB2 was to assess the effect of donanemab versus placebo on clinical progression (i.e., cognitive and functional decline). To capture the complexity of AD, the trial used multiple endpoint measures: both changes in iADRS and CDR-SB scores from baseline to 76 weeks, long-term evaluation, time-based analyses of disease progression risk, disease stability, risk reduction for advancing to the next stage, and delays in progression measured in months. Using several endpoints ensures a sensitive and comprehensive assessment of therapeutic efficacy, allowing detection of clinically meaningful benefits across different dimensions of the disease impact.

Table 6 summarizes the key clinical endpoints in TB2. Additional endpoint results can be found in Appendix B.

Table 6 Key efficacy outcome measures for TRAILBLAZER-ALZ2 and its long-term extension

Outcome measure	Time point[a]	Description	Definition	Validity
Change from BL in iADRS Pivotal trial[b]	Week 76	Assessing the point difference between treatment groups at study endpoint. Percentage slowing of disease progression[c]	linear combination of all ADAS-Cog13 and ADCS-iADL item scores without additional weighting, yielding a total iADRS score from 0 to 144 (lower scores indicate greater impairment).	This assessment is a regulatory requirement for showing effect vs placebo in clinical trials ≥20% slowing of disease considered clinically meaningful (88, 89)
Change from BL in CDR-SB Pivotal trial[b]	Week 76	The same as above.	Semi-structured 75-item interview (~25 min) with patient and informant, rating symptom severity across 6 domains (3 cognitive and 3 functional) using 5 impairment levels (0–3); provides a global CDR score (0–3) for	The same as above. ≥20% slowing of disease (88, 89) or at least 0.5 points (90-92) on the mean change in CDR-SB from BL is considered clinically meaningful

Outcome measure	Time point[a]	Description	Definition	Validity
			dementia stage and a continuous CDR-SB score (0–18) for overall severity.	
CDR-SB change from BL with ADNI matched controls in the LTE Pivotal trial LTE[d]	Week 154	The same as above.	The same as above. As ADNI assessments do not include ADCS-iADL, which is needed for calculating iADRS score, early start and delayed start versus ADNI efficacy analyses focus on CDR-SB.	The same as above.
CDR-G risk of progression to a later clinical stage Pivotal trial[b]	BL to Week 76	Assessing MCID at the individual patient level over the entire study duration	Clinical worsening defined as any increase from BL in the CDR-G score[e] expressed as the risk (HR [95% CI]) of patients meeting the criteria for clinically meaningful worsening of symptoms at 2 consecutive visits	MCID is the threshold used for the evaluation of **individual within patient change over the course of the study** but is not used for interpreting between-group differences at study endpoint (i.e. drug efficacy) (93, 94). It is the threshold at which patient and/or care partner well-being is noticeably impacted.
CDR-SB Risk of meaningful disease progression Pivotal trial[b]	BL to week 76	The same as above.	Clinical worsening (MCID)[f] defined as ≥1-point or ≥2-point decrease for MCI or mild dementia, respectively, expressed as the risk (HR) [95% CI]) of patients meeting the criteria for clinically meaningful worsening of symptoms at 2 consecutive visits	The same as above.

Outcome measure	Time point[a]	Description	Definition	Validity
CDR-SB disease progression delayed Pivotal trial[b]	Week 76	Delay in time to clinical progression. The time difference between treatment and placebo groups to reach a specified point of outcome measure decline is framed as the equivalent of months of time saved with treatment	Expressed as **months of time saved** with donanemab compared with placebo before clinical worsening at a group level within the study timeframe	Contextualizes clinical benefit by assessing between-group differences in time to reach the same level of disease progression
Proportion of participants with amyloid clearance Pivotal trial[b]	Week 24, 52 and 76	Assessing participants who achieved early amyloid clearance and so switched to placebo treatment	Rapid amyloid clearance was defined as amyloid levels of <24.1 CL at Weeks 24 and 52.	

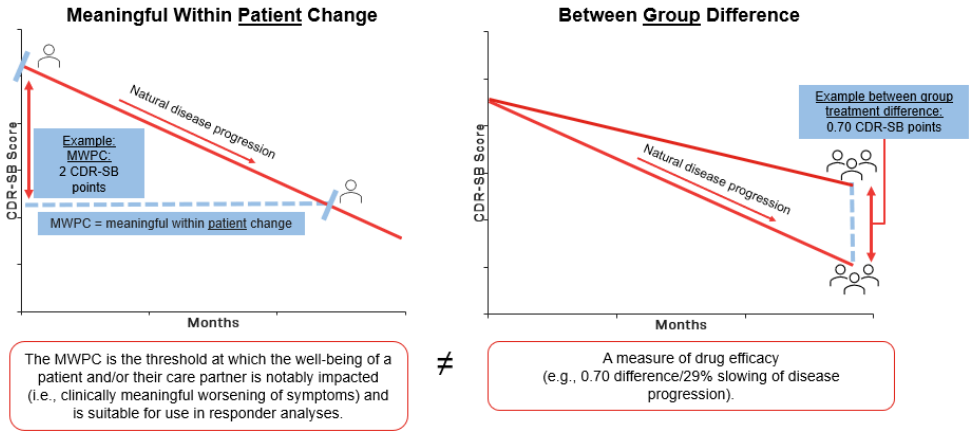
[a] Time point for data collection used in analysis (follow up time for time-to-event measures)
[b] TRAILBLAZER-ALZ2 (NCT04437511) (5)
[c] Calculated as: (LSM change from BL treatment difference at Week 76/LSM change from BL with placebo at Week 76)*100
[d] TRAILBLAZER-ALZ2 (NCT04437511) (6)
[e] MCI due to AD, CDR-G=0.5; mild AD, CDR-G=1; moderate AD, CDR-G=2; severe AD, CDR-G=3 (95-97)
[f] MCID is defined as a MWPC based on ≥1 or ≥2 point worsening on CDR-SB for patients with MCI due to AD or mild dementia due to AD, respectively.

Abbreviations: ADAS-Cog13, Alzheimer's Disease Assessment Scale – Cognitive Subscale; ADCS-iADL, Alzheimer's Disease Cooperative Study – Activities of Daily Living; ADNI, Alzheimer's Disease Neuroimaging Initiative; BL, baseline; CDR-SB, Clinical Dementia Rating Scale – Sum of Boxes; iADRS, Integrated Alzheimer's Disease Rating Scale; LTE, Long-term extension; MMRM, Mixed models for repeated measures; MCID, Meaningful Clinically Important Differences; MWPC, Meaningful Within Patient Change

Clinically important difference in CDR-SB

As outlined in Table 6, it is critical to distinguish between threshold measures of clinical relevance at group level and measures reflecting meaningful within-patient change (MWPC) or minimal important clinical difference (MCID). MWPC/MCID represents the smallest change in an outcome score that a patient or physician considers meaningful and worthwhile. This concept is distinct from the evaluation of treatment efficacy between groups, which assesses average differences between treatment arms, illustrated in Figure 4.

Figure 4. Within patient versus between group differences



Abbreviations: MWPC, meaningful within patient change; CDR-SB, Clinical Dementia Rating Scale – Sum of Boxes- Source: Eli Lilly, Data on File.

The concept of MCID has frequently been misunderstood and misapplied. MCID authors have explicitly stated that these threshold values (≥1-point or ≥2-point decrease for MCI or mild dementia on CDR-SB, respectively) are derived from within-patient estimates, typically anchored to clinician or patient-reported outcomes, and should not be conflated with between-group differences reported in clinical trials (98, 99). MCIDs are intended to provide clinical context for individual patient disease progression, not to serve as regulatory thresholds for assessing group-level treatment efficacy.

Thresholds for clinical relevance between groups have been addressed in an international task force on the design of clinical trials in early AD. The task force concluded that a reduction of at least 0.5 points in the mean change from baseline on the CDR-SB would capture both treatment efficacy and clinical relevance (91, 92). An absolute between-group difference of 0.5 points on the CDR-SB has also been recognized as clinically meaningful by the CHMP in the EU Scientific Advice, 2021 (Lilly Data on file), stating: “A difference in CDR-SB 0.5 point between active and control treatment is in general considered of clinical significance.”

Another threshold measure applied at the group level to assess treatment effects in AD, is the interpretation of treatment differences as a percentage slowing of disease progression compared with placebo (100). Unlike absolute differences, a percentage change is not dependent on the duration of observation and disease stage, and it is generally accepted that ≥20% slowing of disease progression between treatment and placebo groups represents a clinically meaningful effect (88, 89, 101).

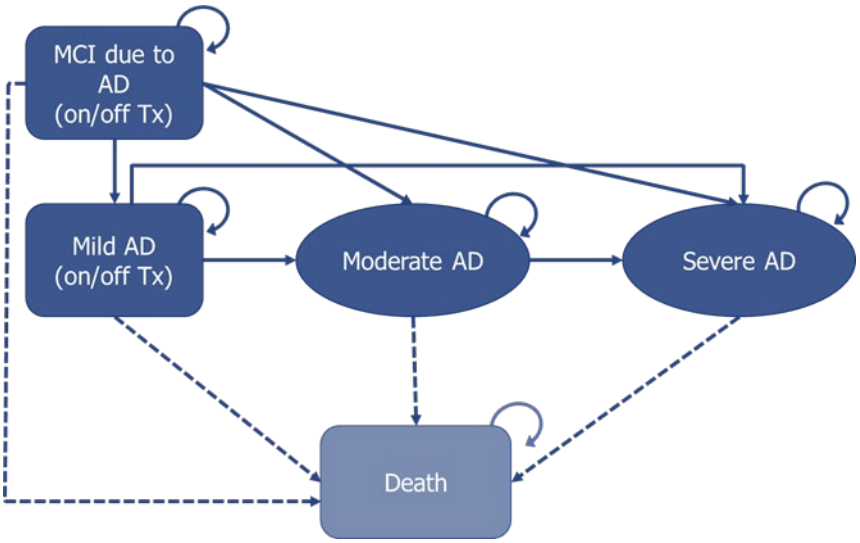
4. Health economic analysis

A cost-utility model was developed to estimate the economic value of donanemab plus BSC for the treatment of early symptomatic AD (i.e. MCI due to AD and mild AD), compared to BSC alone. The information for BSC is presented in Table 88 in Appendix K.

4.1 Model structure

A de novo Markov cohort state-transition model with five health states was developed for the EU eligible patient population to compare donanemab with BSC to BSC alone. The health states are based on disease stages and include MCI due to AD, mild AD, moderate AD, severe AD, and death (Figure 5).

Figure 5 Model structure



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

While alive, patients could be either in a community setting or in residential care. It is assumed that the target patients with MCI due to AD or mild AD are screened before entering the model for eligibility, and as such, diagnostic costs are applied at the beginning of the model. Costs and health state utilities were allocated to each health state and multiplied by state occupancy to calculate the weighted costs and quality-adjusted life years (QALYs) per cycle, which were totaled at the end of the time horizon.

As the nature of AD is a progressive, irreversible disease, patients can only progress to a more severe health state and cannot reverse to the milder state in the base case of the model. Therefore, in each cycle, patients remain in their current state or progress to a more severe health state. A scenario is presented using Potashman et al. data that allow participants to transition to health states that indicate improvement in cognition/function, to explore its impact (see more details in Appendix Q).

Patients either stop treatment according to the fixed treatment duration of 18 months (maximum treatment duration) or due to amyloid plaque clearance at 12 months (73) (more details in Section 8.4). Patients were also assumed to stop receiving donanemab after progressing to the moderate AD health state. Patients could also complete treatment due to AEs. Patients were assumed to continue treatment in residential care.

4.2 Model features

A summary of the model features is described in Table 7.

Table 7 Features of the economic model

Model features	Description	Justification
Patient population	MCI due to AD and mild AD in adult patients that are APOE ε4 heterozygotes or non-carriers. Contraindicated patients in line with the EU SmPC are excluded	There are no deviations from the population described in Section 3.2
Perspective	Limited societal perspective including social care and institutional care cost	According to DMC guidelines
Time horizon	Lifetime (30 years)	Given the nature of AD dementia, a lifetime horizon was deemed necessary to capture all relevant costs and benefits, in line with DMC guidelines
Cycle length	6 months	The cycle length was based on the time interval used for periodic assessment of amyloid clearance in the TRAILBLAZER-ALZ2 trial
Half-cycle correction	Yes	Half-cycle correction has been applied to account for events not occurring at the beginning or end of every cycle
Discount rate	3.5 %	The DMC applies a discount rate of 3.5 % for all years
Intervention	Donanemab + BSC	
Comparator(s)	No addition to BSC	According to national treatment guideline
Outcomes	Change from baseline in CDR-SB (CPH model) at week 76	Whilst iADRS is the primary measure in TRAILBLAZER-ALZ2, CDR-SB is a well-established outcome measure that is widely recognized in AD. Moreover, applying the treatment effect of the CDR to the disease staging based on the CDR increases consistency across the model and reduces uncertainty caused using different scales

Abbreviations: AD, Alzheimer's disease; APOE ε4, apolipoprotein E ε4; BSC, best supportive care; CDR-SB, Clinical Dementia Rating Scale – Sum of Boxes; CHP, Cox proportional hazards model; DMC, Danish Medicines Council; iADRS, integrated Alzheimer's Disease Rating Scale; MCI, mild cognitive impairment.

5. Overview of literature

5.1 Literature used for the clinical assessment

The application is based on the pivotal, placebo-controlled trial with a comparator (BSC + placebo) relevant to Danish clinical practice. The relative efficacy is based on TB2 (5), this section is therefore considered not applicable. However, a clinical SLR was conducted and updated in May 2025. The full report can be provided upon request.

Table 8 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*
Not applicable.				

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

The identified literature used in this application is also summarized in Table 9.

Table 9 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, Ghinai I, Castro Y, Leal J, Roberts N, Wace H. 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. 2020 Dec;12:1-4.	Carer-reported patient health state utilities: MCI due to AD, mild AD, moderate AD, severe AD.	Details are provided in Section 10.
Belger M, Dell'Agnello G, Enstone A, Wyn R, Tockhorn-Heidenreich A. The impact of informal caregiving in Alzheimer's disease dementia: A health utility study in the United Kingdom (PCR24). presented at: ISPOR 27th Meeting; 2022	Child and spousal caregivers' health state utilities: MCI due to AD, mild AD, moderate AD, severe AD. *This study was used as part of a scenario analysis.*	Details are provided in Section 10.

Reference (Full citation incl. reference number)	Health state/Disutility	Reference to where in the application the data is described/applied
Matza L, Howell TA, Belger M, Ritchie C, Delio PR, Johnston JA, Tockhorn-Heidenreich A. Assessment of Health State Utilities Associated With Being a Caregiver for a Person With Alzheimer's Disease With Mild Cognitive Impairment or Dementia. Presented at EU-ISPOR 2024	Child and spousal caregivers' health state utilities: MCI due to AD, mild AD, moderate AD, severe AD. *This study was used as part of a scenario analysis.*	Details are provided in Section 10.

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

5.3 Literature used for inputs for the health economic model

To support assumptions used in the model, as well as model inputs for which data were not collected in TB2, systematic and targeted literature reviews were conducted. The literature used for model inputs in this application is summarized in Table 10.

Table 10 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
Johansson MF, McKee KJ, Dahlberg L, Williams CL, Summer Meranius M, Hanson E, Magnusson L, Ekman B, Marmstål Hammar L. A comparison of spouse and non-spouse carers of people with dementia: a descriptive analysis of Swedish national survey data. BMC geriatrics. 2021 Jun 2;21(1):338.	Caregiver characteristics: Caregivers Per Patient, Proportion of Child Caregivers, Mean Age of Child Caregivers, Proportion of Child Caregivers – females, Proportion of Spouse Caregivers, Mean Age of Spouse Caregivers, Proportion of Spouse Caregivers – females. *This study was used as part of a scenario analysis*	Targeted literature review	Section 12.2

Reference (Full citation incl. reference number)	Input/estimate	Method of identification	Reference to where in the application the data is described/applied
Jönsson L, Tate A, Frisell O, Wimo A. The costs of dementia in Europe: an updated review and meta-analysis. Pharmacoeconomics. 2023 Jan;41(1):59-75.	Direct medical for patient and caregiver health care costs for mild AD, moderate AD, severe AD, in both community and institutionalized settings. Direct non-medical and indirect costs: Patient Social Care Costs, Caregiver Informal Care Costs, Residential care costs, in both community and institutionalized settings.	Targeted literature review	Section 11.4
Skoldunger A, Johnell K, Winblad B, Wimo A. Mortality and treatment costs have a great impact on the cost-effectiveness of disease modifying treatment in Alzheimer's disease-a simulation study. Current Alzheimer Research. 2013 Feb 1;10(2):207-16.	Proportion of costs for patients with MCI versus mild AD	Systematic literature review (economic SLR updated in June 2025 for economic evaluations)	Section 11.4

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

6. Efficacy

6.1 Efficacy of donanemab compared to placebo for MCI due to AD or mild AD dementia patients

6.1.1 Relevant studies

The efficacy and safety of donanemab in symptomatic adults with Aβ pathology and a clinical diagnosis of early symptomatic AD have been evaluated in a robust clinical trial program conducted in accordance with regulatory guidelines for AD studies (102). The program included a broader population (data available upon request) than the EMA-approved label. Therefore, this review considers only clinical outcomes for the EMA approved population, and is referred to as the "EU SmPC population," which excludes ApoE ε4 homozygotes, or the "EU eligible population," which also excludes contraindications from section 4.3 of the EU SmPC[1]. The latter has only been feasible for a subset of endpoints. Nevertheless, it is included, when possible, to more accurately mirror Danish clinical practice and to support the health economic model.

The clinical trial program for donanemab comprised of the following studies:

- TRAILBLAZER-ALZ2 including long-term extension (NCT04437511)
- TRAILBLAZER-ALZ6 (NCT05738486) (TB6)
- TRAILBLAZER-ALZ (NCT03367403)
- TRAILBLAZER-ALZ4 (NCT05108922)
- TRAILBLAZER-EXT (NCT04640077)

The pivotal TB2 trial and its long-term extension, together with TRAILBLAZER-ALZ6 (TB6) informed the assessment of efficacy and safety, while TRAILBLAZER-ALZ, TRAILBLAZER-ALZ4 and TRAILBLAZER-EXT are considered supportive studies; study characteristics are detailed in Appendix A. Latest data cut of TB2, including long-term extension data, was 30 August 2024 (double-blind treatment period of 154 weeks). For TB6, the data cut was 3 April 2025 (double-blind treatment period of 76 weeks). All these data cuts were prespecified.

Analysis methods and statistical approaches
Upon EMAs request, the statistical analysis for the EMA population used a conservative method for the primary and key secondary clinical efficacy endpoints and prespecified method (as per the Statistical Analysis Plan) for other clinical endpoints. The conservative analysis applied multiple imputation for handling missing data with a jump to reference (J2R) method when data was missing for participants with discontinuation due to death or severe, symptomatic, or serious ARIA events, and copy increments in reference (CIR) method used when data was missing for other reasons. Several different statistical approaches were employed in TB2 and specified for each outcome measure. See Appendix N for an overview of these statistical approaches.

[1] Poorly controlled blood pressure defined as systolic blood pressure ≥140mmHg and diastolic blood pressure ≥90mmHg, baseline superficial siderosis or anticoagulant use.

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	Key outcomes and follow-up time (see Appendix A for more endpoint measures)
TRAILBLAZER-ALZ2 (NCT04437511) (5)	Pivotal trial, multicentre, randomised, double-blind trial, phase III study of donanemab versus placebo.	76 weeks	Early symptomatic AD with evidence of Aβ pathology and low-medium or high tau levels.	Donanemab (administered by IV infusion), 700 mg Q4W for the first three doses and 1400 mg Q4W thereafter.	Placebo (administered by IV infusion), Q4W for up to 72 weeks.	**Primary** Change from BL in iADRS (NCS2) at W76 **Secondary** Change from BL in CDR-SB (MMRM) at W76; Proportion of participants with amyloid clearance at W24, W52 and W76 (Fisher's exact test) **Exploratory** CDR-G risk of progression to a later clinical stage (Cox PHM TTE); CDR-SB Risk of meaningful disease progression, BL to W76 (MWPC); CDR-SB disease progression delayed at W76, months saved (Time-PMRM) (Cox PHM TTE)
TRAILBLAZER-ALZ2 LTE (NCT04437511) (6)	Long-term extension of the pivotal trial, double-blind. Unlike traditional extensions of clinical trials and aligned with recommendations in International Council for Harmonization guideline E8 on general considerations for clinical studies, the LTE treatment assignment	78 weeks (W154 in total)	Participants randomized to donanemab in TB2 (early start group[a]) and participants randomized to placebo in TB2 (delayed start group[b]).	Delayed start group: donanemab (administered by IV infusion), 700 mg Q4W for the first three doses, and Q4W thereafter. Few participants from TB2 continued donanemab in the LTE period, but that data	As the placebo participants in the initial phase of the trial initiated donanemab treatment in the extension phase, there was no placebo arm available for comparison in the LTE. Control cohort derived from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database over a 3-year period (see further details in Appendix P).	**Primary** CDR-SB change from baseline with ADNI matched controls at W78 (W154 in total) **Exploratory** Early start versus delayed start in donanemab treatment: impact on the risk of progression on CDR-G score at W78 (W154 in total) Change from BL in amyloid plaque levels, CL (MMRM) at W78 (W154 in total)

Trial name, NCT-number (reference)	Study design	Study duration	Patient population	Intervention	Comparator	Key outcomes and follow-up time (see Appendix A for more endpoint measures)
	was double-blind, hence minimizing the occurrence of conscious or unconscious bias in the conduct and interpretation of the study.			is excluded from all EU analyses, since it is perceived as off label.		
TRAILBLAZER-ALZ 6 (NCT05738486) (7)	Phase IIIb, randomised, double-blind, parallel group, 4-arm study of donanemab different dosing regimens.	Up to 91 weeks including a screening period, double-blind treatment period (76 weeks) and post-treatment follow-up period.	Early symptomatic AD	Standard dose (dosing regimen in TB2) – three doses of 700 mg every 4 weeks, followed by 1400 mg every 4 weeks thereafter (for a total duration of up to 72 weeks)	*Dose skipping* – 700 mg as the first dose, followed by 1400 mg at week 8, and then 1400 mg every 4 weeks thereafter (for a total duration of up to 72 weeks). *Modified titration* – 350 mg as the first dose, then 700 mg as the second dose after 4 weeks, then 1050 mg as the third dose after another 4 weeks, followed by 1400 every 4 weeks thereafter (for a total duration of up to 72 weeks). *Cmax* – six doses of 350 mg every 2 weeks, then two doses of 700 mg every 2 weeks, followed by 1400 mg every 4 weeks thereafter (for a total duration of up to 72 weeks).	**Primary** Proportion of participants with any occurrence of ARIA-E by W24, given the alternative donanemab dosing regimens versus the standard dosing regimen **Secondary** Proportion of participants with any occurrence of ARIA-E by W52; Change from BL in amyloid plaque deposition (PET) at W24, W52, and W76; Proportion of participants with any occurrence of ARIA-H at W24 and W52; ARIA-E and ARIA-H severity.

[a] Participant who initiated donanemab at the start of the initial placebo-controlled phase (TB2)
[b] Participant who initiated donanemab at the start of the LTE



Abbreviations: AD, Alzheimer's disease; TB2, TRAILBLAZER-ALZ2. ADAS-Cog, Alzheimer's Disease Assessment Scale – Cognitive Subscale; ADCS-ADL, Alzheimer's Disease Cooperative Study – Activities of Daily Living; ADNI, Alzheimer's Disease Neuroimaging Initiative; ARIA-E, Amyloid-related imaging abnormality – oedema/effusions; ARIA-H, Amyloid-related imaging abnormality – microhaemorrhage/ haemosiderin deposits; BADL, basic activities of daily living; CDR-SB, Clinical Dementia Ratings Scale – Sum of Boxes; FAQ, Functional Activities Questionnaire; iADL, instrumental activities of daily living; MMSE, Mini-Mental State Examination; NCS2, Natural cubic spline with 2 degrees of freedom; SUVR, Standardised uptake value ratio; Q4W, Every 4 weeks; W76, week 76.

6.1.2 Comparability of studies

As mentioned previously, the clinical efficacy data presented in this application is exclusively informed by TB2, thus this section is not relevant.

6.1.2.1 Comparability of patients across studies

For comparability, Table 12 presents patient characteristics for the overall population (n=1736), EU SmPC population (n=1447) and the EU eligible population (n=1218). Please note, the EU eligible population in Table 12 is including 5 patients with missing APOE ε4 information which were later excluded for efficacy and safety results.

Table 12 Baseline characteristics of patients in studies included for the comparative analysis of efficacy and safety

	Overall (n=1736)		EU SmPC (n=1447)[b]		EU eligible (n=1218)[a]	
	Donanemab (n=860)	Placebo (n=876)	Donanemab (n=717)	Placebo (n=730)	Donanemab (n=614)	Placebo (n=604)
Female sex, n (%)	493 (57.3)	503 (57.4)	414 (57.7)	426 (58.4)	376 (61.2)	358 (59.3)
Mean (SD) age, y	73.0 (6.2)	73.0 (6.2)	73.5 (6.2)	73.7 (6.1)	73.27 (6.25)	73.53 (6.06)
Race, n (%)						
American Indian or Alaska Native	2 (0.2)	0 (0.0)	2 (0.3)	0 (0.0)	1 (0.2)	0 (0.0)
Asian	57 (6.6)	47 (5.4)	49 (6.8)	42 (5.8)	45 (7.3)	31 (5.1)
Black or African American	19 (2.2)	21 (2.4)	16 (2.2)	18 (2.5)	14 (2.3)	13 (2.2)
White	781 (90.9)	807 (92.1)	649 (90.6)	669 (91.6)	553 (90.2)	560 (92.7)
Hispanic/Latino ethnicity (US/Puerto Rico only), n (%)	35 (5.7)	36 (5.7)	29 (5.6)	33 (6.4)	27 (6.2)	26 (6.1)
AChEI/memantine use at baseline, n(%)	521 (60.6)	538 (61.4)	429 (59.8)	451 (61.8)	369 (60.1)	366 (60.6)
AChEI use, n (%)	478 (55.6)	488 (55.7)	390 (54.4)	409 (56.0)	337 (54.9)	334 (55.3)

	Overall (n=1736)		EU SmPC (n=1447)[b]		EU eligible (n=1218)[a]	
	Donanemab (n=860)	Placebo (n=876)	Donanemab (n=717)	Placebo (n=730)	Donanemab (n=614)	Placebo (n=604)
Memantine use, n (%)	172 (20.0)	180 (20.5)	143 (19.9)	157 (21.5)	119 (19.4)	130 (21.5)
Mean (SD) baseline clinical outcome measures						
iADRS score	104.1 (14.3)	103.6 (14.0)	104.3 (14.3)	103.6 (14.2)	104.7 (14.4)	103.5 (14.5)
CDR-SB score	4.0 (2.1)	3.9 (2.1)	4.0 (2.1)	4.0 (2.1)	3.9 (2.1)	4.0 (2.1)
ADAS-Cog13 score	28.7 (8.8)	29.3 (8.9)	28.6 (8.9)	29.1 (9.0)	28.3 (9.0)	29.3 (9.2)
ADCS-iADL score	47.8 (7.9)	47.8 (7.8)	47.9 (7.9)	47.7 (8.0)	48.0 (7.9)	47.8 (8.0)
ADCS-ADL total score	66.3 (8.6)	66.4 (8.3)	66.4 (8.5)	66.2 (8.6)	66.5 (8.5)	66.3 (8.5)
MMSE score[c]	22.4 (3.8)	22.2 (3.9)	22.5 (3.8)	22.1 (3.9)	22.4 (3.9)	22.1 (4.0)
MMSE, category by MMSE at screening, n (%)						
MMSE ≥27	146 (17.0)	137 (15.7)	119 (16.6)	119 (16.3)	97 (15.8)	98 (16.3)
MMSE 20–26	713 (82.9)	738 (84.3)	597 (83.3)	610 (83.7)	516 (84.0)	505 (83.7)
MMSE <20	194 (22.8)	218 (25.1)	1 (0.1)	0 (0.0)	1 (0.2)	0 (0.0)
CDR-G score, n (%)						
0	2 (0.2)	4 (0.5)	2 (0.3)	3 (0.4)	2 (0.3)	2 (0.3)
0.5	514 (60.8)	532 (61.2)	422 (59.8)	439 (60.7)	366 (60.4)	367 (61.2)

	Overall (n=1736)		EU SmPC (n=1447)[b]		EU eligible (n=1218)[a]	
	Donanemab (n=860)	Placebo (n=876)	Donanemab (n=717)	Placebo (n=730)	Donanemab (n=614)	Placebo (n=604)
1	304 (36.0)	308 (35.4)	259 (36.7)	260 (36.0)	219 (36.1)	215 (35.8)
2	25 (3.0)	25 (2.9)	23 (3.3)	21 (2.9)	19 (3.1)	16 (2.7)
Mean (SD) screening amyloid plaque level, CL[d]	103.5 (34.5)	101.6 (34.5)	103.6 (34.5)	102.2 (34.3)	102.6 (34.2)	101.6 (33.6)

[a] EU eligible population includes all randomised participants in TB2 excluding APOE ε4 homozygotes, patients with BL superficial siderosis, poorly controlled blood pressure defined as systolic blood pressure ≥140mmHg and diastolic blood pressure ≥90mmHG and anticoagulant use. 5 patients are included with missing APOE ε4 information.
[b] EU SmPC population includes all randomised participants in TB2 excluding APOE ε4 homozygotes.
[c] Last non-missing MMSE prior to or on start of study treatment.
[d] Assessed with 18F-florbetapir or 18F-florbetaben PET.

Abbreviations: AChEI, acetyl-cholinesterase inhibitor; ADAS-Cog$_{13}$, Alzheimer's Disease Assessment Scale – 13-item Cognitive subscale; ADCS-iADL, Alzheimer's Disease Cooperative Study – instrumental Activities of Daily Living subscale; CDR-G, Clinical Dementia Rating Scale – Global Score; CDR-SB, Clinical Dementia Rating Scale – Sum of Boxes; CL, centiloid; iADRS, integrated Alzheimer's Disease Rating Scale; MMSE, Mini-Mental State Examination; SD, standard deviation.

Source: Sims et al (2023), Solomon (2023), presentation at the Alzheimer's Association International Conference (AAIC 2023), and Jessen (2026).

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

The comparability of the study population with eligible Danish patients is addressed below. Table 13 summarizes the characteristics in the relevant population in Danish clinical practice and the values used in the health economic model.

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

	Value in Danish population[a]	Value used in health economic model (5)
MCI - Age at baseline	70-71 years	70 years, EU eligible population in TB2 has a baseline age of 73.25 years but a Danish KOL confirmed that patients will be younger in Danish setting.
MCI - % of males	Ca 50%	48.2%
MCI - Risk of institutionalisation	0.0%	0.0%
Mild - Age at baseline	70-71	70 years, EU eligible population in TB2 has a baseline age of 73.24 years but a Danish KOL

		confirmed that patients will be younger in Danish setting.
Mild - % of males	Ca 50.0%	39.9%
Mild - Risk of institutionalisation	0.0%	0.0%
Proportion MCI	KOL input suggests that patients first to be treated in Denmark will be early in the disease spectrum (103)	50% (to match patients first to receive treatment in clinical practice)
Proportion mild AD	-	50% (calculated)

[a]validated with a Danish KOL (34)
Abbreviations: AD, Alzheimer's disease; MCI, mild cognitive impairment; TB2, TRAILBLAZER-ALZ2; KOL, key opinion leader.

Note: The model allows the user to vary the risk of institutionalization in the Disease Progression sheet.

6.1.4 Efficacy – results per TRAILBLAZER-ALZ2 including its long-term extension

iADRS and CDR-SB – change from baseline to Week 76

In TB2, treatment with donanemab demonstrated a consistent and clinically meaningful slowing of disease progression across cognitive, functional, and global clinical endpoints. Treatment effects were evident on both the iADRS and CDR-SB at Week 76, demonstrating a statistically significant slowing of disease progression compared with placebo (Table 14). For a figure presentation, see Figure 26 and Figure 27 in Appendix O. The observed effects both approach or exceed the clinically meaningful threshold of 20% slowing of disease progression, supporting the conclusion that donanemab provides clinically meaningful benefit in the EU SmPC and EU eligible population.

Importantly, a statistically significant separation from placebo on the CDR-SB was evident as early as Week 12 (EU SmPC p=0.0102; EU eligible p=0.0045), with increasing treatment effects over time (EU SmPC -0.30 at Week 24, -0.56 at Week 52, –0.69 at Week 76; EU eligible -0.31 at Week 24, -0.57 at Week 52, and -0.67 at Week 76). Already from Week 52 the differences exceed the established threshold for clinical meaningfulness, defined as an absolute difference of ≥0.5 points on the CDR-SB (91, 92).

Table 14 Donanemab vs. Placebo at Week 76 in TRAILBLAZER-ALZ2: Key Endpoints for the EU SmPC- and EU eligible population

Endpoint	Population	LSM difference vs PBO, (95% CI)	Slowing disease progression, % (95% CI)	p-value vs PBO
Change from BL to W76 in iADRS[a]	EU SmPC	2.65 (1.04, 4.26)	19.6% (7.59, 31.69)	p=0.0013
	EU eligible	2.32 (0.69, 3.95)	17.9% (5.22, 30.58)	p=0.0053
Change from BL to W76 in CDR-SB[a]	EU SmPC	-0.69 (-0.95, -0.43)	28.5% (17.44, 39.51)	p <0.0001
	EU eligible	-0.67 (-0.97, -0.37)	28.2% (15.18, 41.29)	p <0.0001

[a]Analysis method: Conservative J2R/CIR (MMRM)

Abbreviations: CDR-SB, Clinical Dementia Rating Scale – Sum of Boxes; iADRS, integrated Alzheimer's Disease Rating Scale; CIR, copy increment reference; J2R, jump to reference method; LSM, least squares mean; MMRM, mixed models for repeated measures. BL, baseline; PBO, placebo. Source: Kisunla EPAR and Eli Lilly, Data on File.

CDR-SB domains

CDR-SB domains include memory, orientation, judgment and problem solving, community affairs, home and hobbies, and personal care. These are truly meaningful daily measures experienced by patients with AD and reflected by care partners. The reduction in the CDR-SB score at Week 76 observed with donanemab treatment in the EU SmPC population was accompanied by statistically significant changes across all six cognitive and functional domains of the CDR-SB. This indicates slowing of disease progression with donanemab, translating into meaningful benefits for patients and those that provide support (Table 15).

Table 15 Treatment effect of donanemab across individual CDR-SB domains in the EU SmPC population at Week 76[a,b]

	CDR-SB domain	LSM difference vs PBO, (95% CI)	% Slowing	p-value vs PBO
Cognition	Memory	–0.12 (–0.18, –0.06)	30.4%	<0.0001
	Orientation	–0.09 (–0.15, –0.03)	24.4%	0.0028
	Judgement and problem solving	–0.10 (–0.16, –0.04)	31.0%	0.0006
Function	Community affairs	–0.07 (–0.13, –0.01)	17.4%	0.0201
	Home and hobbies	–0.13 (–0.20, –0.07)	29.6%	<0.0001

CDR-SB domain	LSM difference vs PBO, (95% CI)	% Slowing	p-value vs PBO
Personal care	–0.11 (–0.18, –0.04)	33.9%	0.0020

[a] Analytical method: Conservative J2R/CIR
[b] Statistical method: Mixed models for repeated measures (MMRM)

CDR-SB, Clinical Dementia Rating Scale – Sum of Boxes; CI, confidence interval; CIR, copy increment reference; J2R, jump to reference method; LSM, least squares mean

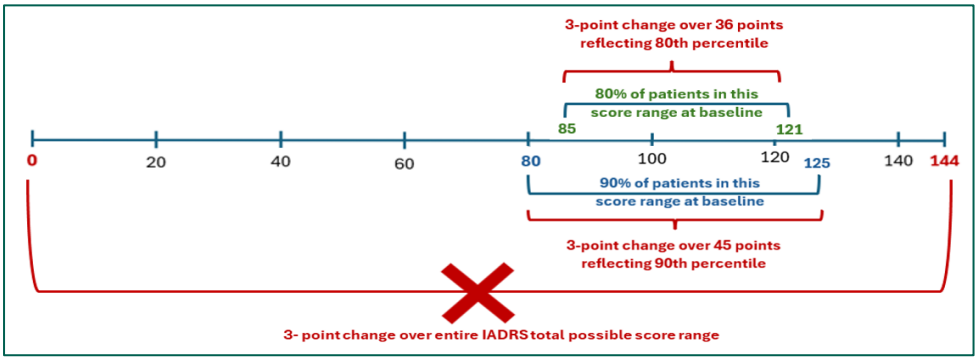
Source: Eli Lilly, Data on File.

Baseline iADRS and CDR-SB percentiles: additional context for change in results

When assessing clinically meaningful change, it is important to note that both the iADRS and CDR-SB scales have a wide range because they are intended to capture the disease continuum (i.e. from no impairment to severe AD). The iADRS scale range is 0-144. However, only a small portion of the iADRS scale is relevant for the interpretation of treatment effects in patients with MCI or mild dementia due to AD. Therefore, this dynamic range (not the full 0-144 range) should be considered when interpreting whether a ~3 point change is clinically meaningful. At baseline in TB2, 80% of individuals in the EU SmPC population fell within a range of 36 points on iADRS, covering only about one quarter of the total score range, see Figure 6 including a describing of the 10th and 90th percentiles or the 5th and the 95th percentiles.

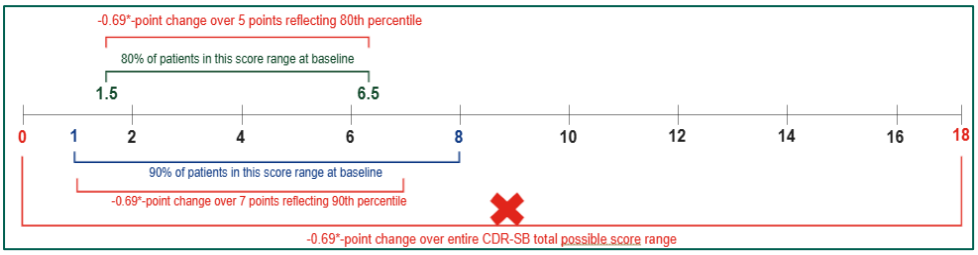
Similarly, the CDR-SB scale range is 0 to 18. However, majority of patients (80%) fall within a range of 5 points, covering about a 1/4 of the total score range, or 90% of patients fall within a range of 7 points, covering approximately 1/3 of the total score range at baseline (see Figure 7). So, when evaluating treatment effects using the iADRS and the CDR-SB scale in patients with MCI or mild dementia due to AD, it is crucial to focus on the dynamic range relevant to this population rather than the full scale. Most individuals at baseline fall within a limited portion of the total score range, so even modest changes, such as a difference of around 3 points on iADRS or -0.69 points on the CDR-SB, can represent a clinically meaningful improvement.

Figure 6 IADRS score range at baseline in the EU SmPC population of TRAILBLAZER-ALZ2



Source: Eli Lilly, data on file.

Figure 7 CDR-SB score range at baseline in the EU SmPC population of TRAILBLAZER-ALZ2



Note: Score of [0,4] indicates MCI, [4.5, 9] mild AD, [9.5,15.5] moderate AD, score >16 severe AD. Source: Eli Lilly, Data on File.

Time-based endpoints (baseline to Week 76)

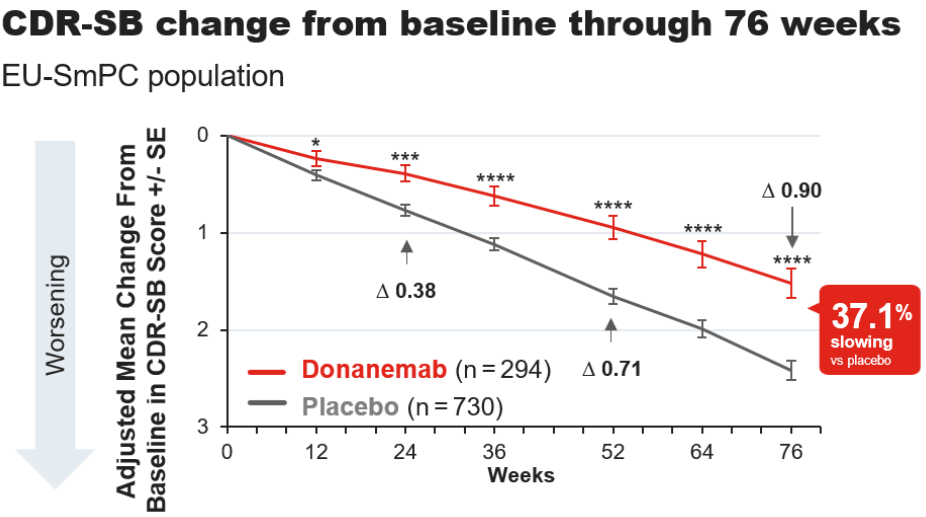
Several prespecified time-based analyses were conducted as exploratory endpoints in TB2 to evaluate the risk of disease progression and time to clinical worsening. These risk-of-progression analyses differ from previously presented outcomes in that they evaluate individual within-patient change using data from all available time points. As such, they provide insight into the clinical meaningfulness of treatment effects at the individual patient level, rather than average effects observed at the study population level. Importantly, the results should still be interpreted as between-group differences with those thresholds for clinical meaningfulness.

Additional data on a response-guided, time-limited strategy

A post-hoc, sub-group analysis from TB2 evaluated the outcomes among participants who completed treatment following confirmed amyloid plaque clearance and switched to placebo at 24 or 52 weeks[2]. Results are presented in Figure 8 and demonstrate continued separation from placebo through Week 76, with effect sizes comparable to those observed in participants receiving donanemab treatment for the maximum treatment duration of 18 months, which could support at response-guided, time-limited treatment approach (Section 3.4.2).

[2] Conservative analysis method.

Figure 8 CDR-SB change from baseline through 76 weeks in donanemab participants who switched to placebo



Notes: If the amyloid plaque level was <11 Centiloids on a single PET scan or <24.1 Centiloids on 2 consecutive PET scans, it was considered cleared, and the patient was eligible to be switched to placebo.
*Nominal P-values: P<0.001.
Abbreviations: APOE ε4=Apolipoprotein E type ε4 Allele; CDR-SB=Clinical Dementia Rating Scale–Sum of Boxes; N=Number of Participants; P=Probability value; SE=Standard Error. Source: Jessen et al, 2026, Supplementary

Risk of progression to next disease stage and risk of meaningful within-participant disease progression

Another important clinically meaningful change measured was the risk of advancing to the next stage of disease. Progression was measured using the CDR-Global score[3] (definition from Table 6), with clinical worsening defined as any per patient increase in CDR-G score from baseline at two consecutive visits. In both the EU SmPC and EU eligible population donanemab-treated participants were at a significantly lower risk of progressing to the next disease stage over the course of the study compared with placebo. The observed reduction in risk of progression suggests that donanemab allows patients to spend more time in earlier disease stages, a benefit that extends beyond clinical measures to broader societal impact. This aligns with the European Alzheimer's Disease Consortium (EADC) position statement, which highlights that from a societal perspective, reducing the risk of disease stage advancement is particularly important given the steep increase in care-related costs with advancing stages of AD (104).

Consistent with the stage-based findings, donanemab also demonstrated a clinically meaningful slowing of disease progression at the individual patient level, as measured by the risk of meaningful within-participant change (MWPC) on the CDR-SB.
In both the EU SmPC and EU eligible population, donanemab significantly reduced the risk of reaching the defined thresholds (definition from Table 6) compared with placebo, indicating that fewer treated participants experienced clinically relevant worsening over time. It is worth noting that the meaningful slowing of disease progression translated into a number needed to treat (NNT) of 8.4, which means that for every 8 patients treated with donanemab, 1 patient will not experience clinically meaningful worsening of

[3] CDR-G scores range from 0 (normal) to 3 (severe dementia).

symptoms because of the treatment. This estimate should be interpreted as contextual rather than predictive at the individual level.

Together, the CDR-G and CDR-SB time-to-event analyses provide consistent evidence that donanemab delays both structural disease stage transitions and clinically meaningful deterioration experienced by individual patients, reinforcing the robustness and real-world relevance of the treatment effect (Table 16). Figure 35 in Appendix O demonstrates the EU SmPC population result for CDR-G risk of progression to a later clinical stage BL to W76.

Table 16 Time-based endpoints for the EU SmPC and EU eligible population (BL to Week 76)

Endpoint	Population	LSM difference vs PBO, (95% CI)	Lower risk of disease progression	p-value vs PBO
CDR-G risk of progression to a later clinical stage BL to W76[a]	EU SmPC[c]	HR 0.597 (0.47, 0.75)	40.3%	<0.0001
	EU eligible[d]	HR 0.53 (0.30, 0.92)	47.2%	0.0238
CDR-SB Risk of meaningful disease progression BL to W76[b]	EU SmPC[c]	HR 0.64 (0.52, 0.78)	36.4%	<0.001
	EU eligible[d]	HR 0.62 (0.49, 0.78)	38.0%	<0.001

[a] Statistical method: (Cox PHM TTE)
[b] Statistical method: (MWPC) (Cox PHM TTE)
[c] Analysis method: Prespecified
[d] Analysis method: Prespecified, post-hoc population

Abbreviations: BL, baseline; CDR-G, Clinical Dementia Rating Scale – Global score; CDR-SB, Clinical Dementia Rating Scale – Sum of Boxes; CI, confidence interval; Cox-PHM, Cox proportional hazards model; TTE, Time-to-event HR, hazard ratio; LSM, least squares mean; MWPC, meaningful within-patient change; PBO, placebo. Source: Kisunla EPAR and Eli Lilly, Data on file.

Slowing of disease progression expressed as time saved (EU SmPC population only)
Using a time-progression model for repeated measures, treatment with donanemab was associated with a statistically significant delay in disease progression at 76 weeks compared with placebo in the EU SmPC population, as measured by the CDR-SB (Table 17). The results suggest that patients treated with donanemab for either 6 or 12 months (following amyloid plaque reduction to minimal levels) or 18 months experience a delay in disease progression corresponding to approximately 6 months of time saved.

Table 17 Delay in disease progression measured as time saved assessed by CDR-SB

Endpoint	Population	Months saved vs PBO, (95% CI)	Time saved (95% CI)	p-value vs PBO
CDR-SB disease progression delayed at W76[a]	EU SmPC[b]	5.82 (4.2, 7.44)	33.17% (23.95, 42.4)	<0.001

[a] Proportional time-PMRM analysis result was used for CDR-SB. The time-PMRM test for proportionality assumes proportionality *a priori*. The test found that the *a priori* assumption was not rejected (p=0.266 from a likelihood ratio test [the *a priori* assumption is not rejected if the associated p-value is above 0.05, and so the proportionality analysis results can be used]).

[b] Analysis method: Prespecified

CDR-SB, Clinical Dementia Rating Scale – Sum of Boxes; CI, confidence interval; DON, donanemab; PBO, placebo; BL, baseline, W76, week 76; W52, week 52; PMRM, progression model for repeated measures. Source: Kisunla EPAR.

Biomarker endpoint: Amyloid plaque clearance

Two definitions are used in this dossier, and they serve different purposes.

1. SmPC definition (clinical practice and health economic model). Treatment is stopped when amyloid plaque clearance, defined as <24.1 CL (a negative visual read on amyloid PET) is confirmed. This is the definition used in the health economic model, which stops treatment at Month 12 according to the proportion of patients with clearance <24.1 CL at Week 52 in the EU eligible population in TB2 (69.7%; Table 18). The model is intended to reflect how donanemab will be used in Danish clinical practice.

2. TB2 stopping rule. The TB2 study was designed to allow participants to complete donanemab treatment and switch to placebo in a double-blind manner once prespecified amyloid plaque clearance thresholds (<11 CL on any one measure or <24.1 CL at two consecutive measures) and time points (Weeks 24 or Week 52) were reached (5). The rule gave a uniform and prespecified definition of treatment stop within a double-blind trial. It is more restrictive than the SmPC definition: no participants met the two-scan alternative at week 24, so fewer participants met the stopping rule than has clearance <24.1 CL at the same time points. In the EU SmPC population, 294 participants met the TB2 stopping rule and switched to placebo at Week 24 or Week 52. Their clinical course after treatment stop is shown in Figures 8 and 9.

The proportion of participants who would stop treatment according to the SmPC definition (<24.1 CL), as applied in Danish clinical practice, and of participants who met the TB2 stopping rule are presented at Week 24, 52 and 76 weeks in Table 18. For a figure presentation, see Figure 30 and Figure 31 in Appendix O.

Table 18 Proportion of participants with amyloid plaque clearance at Week 24, Week 52 and Week 76

Endpoint	Population	Amyloid clearance donanemab[a] per SmPC defined and Danish clinical practice stopping rule (95% CI)	p-value	Amyloid clearance donanemab per TB2 stopping rule
Proportion of participants with amyloid plaque clearance[b] at W24[c]	EU SmPC[d]	32.5% (29.01, 36.29)	<0.0001	18.8%
	EU eligible[e]	33.5% (29.63, 37.51)	<0.0001	NR
Proportion of participants with amyloid plaque clearance[b] at W52[c]	EU SmPC[d]	69.5% (65.59, 73.18)	<0.0001	46.2%
	EU eligible[e]	69.7% (65.45, 73.55)	<0.0001	NR
Proportion of participants with amyloid plaque clearance[b] at W76[c]	EU SmPC[d]	80.8% (77.15, 83.95)	<0.0001	64.1%
	EU eligible[e]	80.5% (76.58, 83.88)	<0.0001	NR

[a] Placebo across all endpoints ranged from 0.0-0.2%
[b] Amyloid plaque clearance defined as a level of <24.1 CL, which equates to a negative visual read on an amyloid PET scan.
[c] Statistical method: Fisher's exact test
[c] Analysis method: Prespecified
[e] Analysis method: Prespecified, post-hoc population
[f] Amyloid plaque clearance defined as a level of <11 CL on any one measure or <24.1 CL at two consecutive measures
Abbreviations: W24, week 24; W52, week 52; W76, week 76. Source: Kisunla EPAR and Eli Lilly, Data on file.

TRAILBLAZER-ALZ2 Long-Term Extension (LTE) Study

CDR-SB change from baseline with ADNI matched controls[4], through 154 Weeks (EU SmPC population only[5])

The double-blinded LTE of TB2 was conducted to evaluate durability of clinical benefit after completion of donanemab treatment as well as any benefit from earlier treatment initiation. An ADNI-matched external control cohort was used as the only ethically permissible and regulatorily recognized comparator for the TB2-LTE follow-up. This was because a conventional placebo-controlled extension beyond 18 months was not ethically feasible following demonstration of significant clinical benefit in the primary

[4] As the placebo participants in the initial phase of the trial initiated donanemab treatment in the extension phase, clinical changes assessed by the CDR-SB was compared to a propensity matched control cohort derived from the ADNI database over a 3-year period. Using propensity score weighting, the decline on the CDR-SB in the ADNI control cohort closely matched the trend in the placebo arm of TRAILBLAZER-ALZ2 18-month data (see Figure 20 in Appendix O).

[5] Analysis is not available for the EU eligible population due to ADNI not collecting key information to mimic this subpopulation.

trial. In accordance with the Declaration of Helsinki, continued assignment of participants to placebo is considered unethical once there is good evidence supporting the efficacy of the trial therapy, particularly for serious and progressive conditions such as AD (105). Furthermore, the EMA guideline on clinical investigation of medicines for the treatment of AD explicitly requires the design of long-term efficacy and maintenance of effect studies and recognizes delayed-start designs as appropriate methodologies for demonstrating disease modification (CPMP/EWP/553/95 Rev.2, Sections 8.3.2 and 11.2) (106).

These ethical considerations directly informed the categorization and analysis of participants in the LTE, shaping the study design to compare early- and delayed-start groups and to ensure meaningful, long-term insights into donanemab's clinical efficacy. Participants were thus categorized as early-start participants[6] and delayed-start participants[7,8]. The results showed that treatment effect of donanemab extended beyond the 18-month treatment period, with the absolute difference between treatment arms increasing between 18 and 36 months. Both early-start participants (Figure 33 in Appendix O) and delayed-start participants (Figure 34, Appendix O) had clinically meaningful benefit from donanemab treatment, with early treatment initiation associated with greater benefit (Table 19).

Table 19 TRAILBLAZER-ALZ2 Long-Term-Extension in the EU SmPC population; Donanemab versus Weighted ADNI Cohort up to 36 Months

Endpoint	Trial population	DON vs ADNI difference (95% CI) 18 months	DON vs ADNI difference (95% CI) 36 months	p-value
CDR-SB change from BL with ADNI[b] matched controls in the LTE	Overall	-0.57 (-0.94, -0.21)	-0.97 (-1.52, 0.42)	<0.001
	Early start	-0.6 (-0.9,-0.2)	-1.0 (-1.5, 0.4)	<0.001
	Delayed start	0.0 (-0.4, 0.4)[a]	-0.6 (-1.2, -0.0)	<0.001

[a]Participants in the delayed start group were placebo recipients from TB2 who began donanemab after 18 months, resonating with no difference (0.0) between groups at this timepoint.
[b]ADNI cohort was weighted using Propensity Score using Average Treatment effect on the treated (ATT) weight; CDR-SB change from baseline were estimated with MMRM model using ADNI weights (see more information in Appendix P).
Abbreviations: CDR-SB, Clinical Dementia Rating Scale – Sum of Boxes; CI, confidence interval; DON, donanemab; BL, baseline, ADNI, Alzheimer's Disease Neuroimaging Initiative; LTE, long-term extension. Source: Eli Lilly, Data on file.

[6] Participant who initiated donanemab at the start of the initial placebo-controlled phase

[7] Participants who initiated donanemab at the start of the LTE

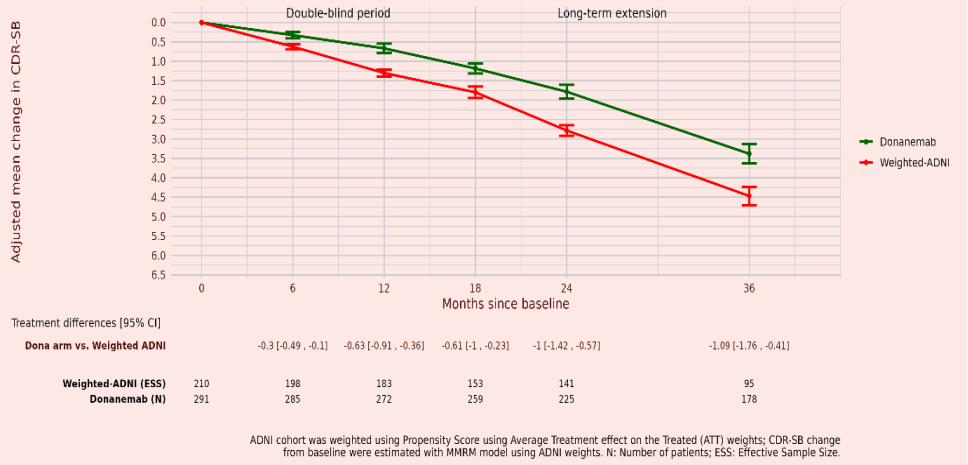
[8] Notably, a different weighting procedure of the ADNI participants was conducted for the delayed start patient analysis. The different weighting system explains why the effective sample sizes are different between the comparisons versus Donanemab early start (ESS=210) and Donanemab delayed start (ESS = 234). The ADNI participants informing the external control arm for the delayed start analysis is a subset of the patients considered in the early start analysis weighted ADNI cohort.

Building on the findings, which established that participants receiving donanemab experienced consistent clinical improvement compared to the ADNI matched control group throughout the three-year follow-up, a detailed analysis of subgroup outcomes based on treatment duration and switching to placebo was performed. Among the early-start cohort, 294 transitioned to placebo in a blinded manner after 6 and 12 months, respectively, offering insight into the durability of treatment effects. Thus, to further assess the long-term impact of donanemab, sensitivity analyses were conducted for participants who switched to placebo after meeting treatment completion criteria. This evaluation included two distinct subgroup analyses: one combining participants who switched to placebo at either 6 or 12 months (utilizing the same donanemab cohort as depict in Figure 8), and another focusing on participants who switched at 12 months only.

The results for the combined subgroup of participants who switched at 6 or 12 months are illustrated in Figure 9. This shows an absolute difference in clinical outcomes between the donanemab-treated groups and controls, with the gap widening from 18 to 36 months. Additionally, analysis of the subgroup of participants who completed 12 months of treatment and then switched to placebo showed a doubling of the CDR-SB treatment effect between 18 and 36 months (see Figure 32 in Appendix O). These findings indicate that donanemab delivers sustained, disease-modifying benefits with positive effects continuing after treatment has ended. The increasing separation between groups from 18 to 36 months underscores the lasting efficacy of donanemab, regardless of whether participants switched to placebo at 6 or 12 months, while the 12-month switchers alone demonstrate particularly robust and durable benefit.

The early-start participants who met the prespecified amyloid PET-based stopping criteria switched to placebo under continued blinding and remained on placebo throughout the LTE; the infusions they received in the LTE were placebo infusions.

Figure 9 TRAILBLAZER-ALZ2 Long-Term-Extension; Donanemab versus Weighted ADNI Cohort up to 36 Months in SmPC population switching to Placebo at Month 6 or 12



Abbreviations: ADNI = Alzheimer's Disease Neuroimaging Initiative; CDR-SB = Clinical Dementia Rating – Sum of Boxes; ESS = effective sample size; LTE = long-term extension; TB2 = TRAILBLAZER-ALZ2. Source: Jessen et al, 2026, supplement (54)

Those results were consistent and led to similar interpretation for the overall EU SmPC population, regardless of the weighting method used. No statistically significant differences in CDR-SB change from baseline were observed between the TB2 placebo and weighted ADNI cohort at 18 months, as shown in Figure 36 in Appendix O, which supports the use of the weighted ADNI cohort as an external control arm for the TB2 LTE. In conclusion, statistically significant differences are observed at month 36 in CDR-SB change from baseline between donanemab-treated participants and the weighted ADNI external control arm for all analyses and populations supporting our cost-effectiveness modelling approach of continuous treatment effect after patients compete donanemab treatment.

Amyloid plaque re-accumulation in the TRAILBLAZER clinical trial program

Following completion of donanemab treatment if amyloid plaque is cleared from the brain, analyses from the TB2-LTE demonstrated sustained reductions in amyloid plaque burden over the entire study duration. Specifically, mean amyloid levels in the EU SmPC population remained below the predefined clearance threshold of 24.1 Centiloids (consistent with a negative visual read on an amyloid-PET scan (107)) at 36 months among participants who completed donanemab treatment already at 24 weeks or 52 weeks (Figure 37 in Appendix O) (108).

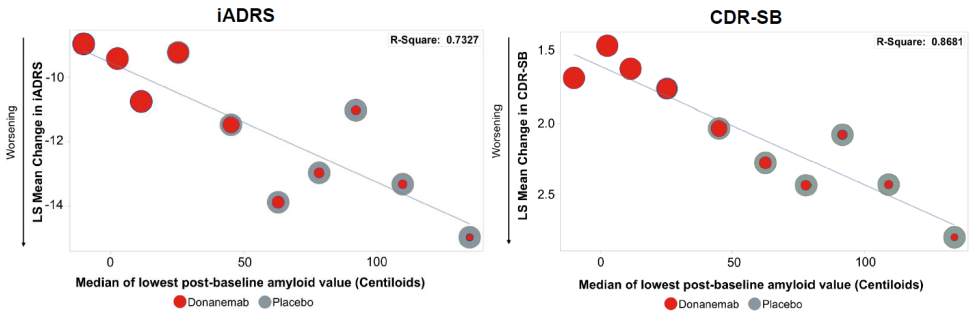
Observed data across four donanemab studies, including a Phase 1 trial (NCT02624778) (109), TRAILBLAZER-ALZ, TRAILBLAZER-EXT Parts B and C (NCT03367403, NCT04640077), and TRAILBLAZER-ALZ2 + LTE (NCT04437511), showed that amyloid plaque re-accumulation after treatment completion occurred at a rate of 2.4 CL/year, as predicted by an exposure-response model based on up to 3 years of data. This rate is consistent with the natural amyloid accumulation rate, which is estimated at ~3.3 CL/year (110, 111). Evidence is thus proposing that amyloid plaque re-accumulation is slow following treatment completion and that donanemab treatment could place patients on a plaque accumulation trajectory comparable to that observed in non-treated amyloid-negative individuals or even slightly lower (108, 112).

Relationship between amyloid plaque reduction and clinical outcomes

Supporting the above, findings across clinical trials of amyloid-targeting therapies suggest that reductions in amyloid plaque burden is associated with clinical benefit (113). While long-term data are currently limited for donanemab to 3 years based on the TB2 LTE, data on amyloid levels and amyloid re-accumulation rates can be used as a surrogate to extrapolate treatment effect beyond the observed clinical follow-up period. Figure 10 shows the iADRS and CDR-SB outcomes from the TB2 trial. Participants were categorized into deciles based on their lowest post-baseline amyloid plaque values, and the median amyloid level within each decile was calculated. Correlations were assessed between median amyloid levels and LS mean changes in clinical outcomes (CDR-SB or iADRS). Across both clinical endpoints, greater clinical worsening was observed in deciles with higher median post-baseline amyloid levels, whereas lower amyloid levels were correlated with less disease progression at 18 months. These findings support an association between amyloid plaque burden and clinical decline, indicating that more robust amyloid clearance is associated with greater clinical benefit following donanemab treatment (114). Together, these results support the use of amyloid plaque reduction as

a surrogate measure to inform long-term extrapolation of clinical treatment effects. Amyloid is, however, one of several drivers of disease progression, including tau. The large effect on amyloid plaque is therefore not mirrored by an equally large effect on cognitive function, and proportionality is not the appropriate requirement.

Figure 10 Bubble Plot of iADRS and CDR-SB by Amyloid Level in TRAILBLAZER-ALZ2



Abbreviations: CDR-SB: Clinical Dementia Rating Scale-Sum of Boxes; LS: least-square. Source: (114) and Eli Lilly, Data on file.

Outcome measures supporting a response-guided, time-limited strategy

Collectively, the presented data indicate that donanemab, which targets insoluble amyloid plaque deposits in the brain, enables time-limited treatment. Although LTE data are generally associated with methodological limitations, as also noted by the Danish National Knowledge Centre for Dementia, the Centre nevertheless concludes that the long-term efficacy observed with donanemab is convincing. The Centre further notes that amyloid-targeting therapies differ in their mechanisms of action, and that participants treated with donanemab solely, can sustain amyloid clearance for longer periods (115). However, the Centre appears to have overlooked a key methodological distinction between the LTE study designs of amyloid-targeting therapies. Specifically, the donanemab extension study was conducted under continued double blinding, including a blinded switch from active treatment to placebo following amyloid plaque clearance. This design reduces the risk of expectancy and assessment bias in long-term clinical outcome evaluation and enables a more robust assessment of the durability of clinical effects after treatment completion, compared with LTEs conducted using an open-label design.

So, with careful disease monitoring, chronic therapy may not be necessary. A donanemab regimen that is response-guided and time-limited has the potential to reduce treatment burden for patients, families, and healthcare systems, reduce the risk of adverse events, and reduce costs in a real-world setting.

Data on study discontinuation

In the TB2 overall population, discontinuation of the study due to AEs occurred in 69 participants (8.1%) in the donanemab group compared with 32 participants (3.7%) in the placebo group. Discontinuation of treatment due to AEs was reported in 112 participants (13.1%) in the donanemab group and 38 participants (4.3%) in the placebo group.

In the EU SmPC population, 54 participants (7.6%) in the donanemab group and 21 patients (3.5%) in the placebo group discontinued the study due to AEs. Discontinuation

of treatment due to AEs occurred in 73 patients (12.0%) in the donanemab group and 22 patients (3.6%) in the placebo group.

In the EU eligible population, there were 39 participants (6.4%) in the donanemab group and 26 participants (3.6%) in the placebo group who discontinued the study due to AE. 91 participants (12.8%) in the donanemab group and 28 participants (3.8%) in the placebo group discontinued treatment due to AE.

7. Comparative analyses of efficacy

7.1.1 Differences in definitions of outcomes between studies

Not applicable.

7.1.2 Method of synthesis

Not applicable.

7.1.3 Results from the comparative analysis

Since the health economic model uses the EU eligible population as its basis, the primary outcomes for this group are shown in Table 20.

Table 20 Results from the comparative analysis of donanemab vs. placebo for EU eligible population (between group comparison)

Outcome measure	Donanemab (n=612)	Placebo (n=601)	Result (95% CI)
Change from baseline to Week 76 in iADRS	-10.64 (0.60)	-12.95 (0.59)	17.9% (5.22, 30.58)
Change from baseline to Week 76 in CDR-SB	1.70 (0.108)	2.37 (0.116)	28.2% (15.18, 41.29)

Abbreviations: CDR-SB, Clinical Dementia Rating Scale – Sum of Boxes; iADRS, integrated Alzheimer's Disease Rating Scale. Source: Eli Lilly, Data on file.

7.1.4 Efficacy – results per [outcome measure]

Not applicable.

8. Modelling of efficacy in the health economic analysis

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

In this application, a Markov structure of the model was deemed most appropriate and data on transition probabilities across the AD disease spectrum (particularly to reflect the transitions in an amyloid-positive AD dementia cohort) needed to be identified. Thus, a study was initiated during the model conceptualization stage to generate robust estimates of the annual probabilities of transitioning between various AD dementia health states across the full disease spectrum, based on the publicly available longitudinal data from the National Alzheimer's Coordinating Center (NACC) Uniform Data Set (UDS). The primary objective of the study was to estimate annual transition probabilities from one disease stage to a more advanced stage among a recent prevalent cohort of participants with biomarker-confirmed early AD. The primary strength of these transition probabilities is that they are based on a biomarker-confirmed AD population which is known to differ from that of a general MCI-dementia population typically found in local data sources. However, the NACC analysis did not allow for estimation of age-dependent transition probabilities which may be seen as a limitation. Although increasing age is a strong risk factor for dementia which may imply that the conversion rates (from MCI to dementia) are expected to increase with age, the available evidence suggests a more complex picture. A recent meta-analysis showed that the increased risk of conversion due to amyloid-positivity actually decreased with age (116), which suggests that the age-effect in persons with MCI due to AD is weaker than in those with MCI due to other causes. For this reason, we opted for constant transition probabilities independent of age but based on a biomarker-confirmed AD population.

In absence of local data on institutionalization risk, this was obtained from Knapp et al. based on a study from greater London (117). See more information about NACC data and other sources that were explored in Appendix M and in Section 8.1.2.

8.1.1 Extrapolation of efficacy data

Not applicable.

8.1.1.1 Extrapolation of [effect measure 1]

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

Method/approach	Description/assumption
Not applicable.	

8.1.2 Calculation of transition probabilities

In the model, the natural history of disease progression is informed by transition probabilities between health states defined on the CDR-SB scale using a cohort of prevalent cases (n=3,334) in line with routine clinical practice. Data from NACC were used to estimate annual transition probabilities among recent prevalent cohorts of individuals with biomarker-confirmed early AD dementia using CDR-SB; transition probability calculations did not allow participants to experience an improvement in their disease. These probabilities were rescaled to the 6-month model cycle length as follows:

- The probability of transitioning out of any given state was converted to an exponential rate that was scaled to align with the cycle length
- The scaled rates were then reconverted to the probabilities
- The probabilities for remaining in the same state (i.e., the probabilities on the principal diagonal of the trace matrix) were calculated as the difference between 100% and the row sums of scaled probabilities to ensure that the transition probabilities from each state sum to 100%
- The transition matrix was recalculated for each comparator and for each timepoint in the calculations to account for the varying probability of death based on the patient's age (described in Section 8.4).

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

The analysis on transition probabilities across the AD disease spectrum did not include the probabilities for transition to the institutionalization setting, which were sourced from Knapp et al. (Table 22). In an attempt to obtain a local source, alternative probabilities for transition to the institutionalization setting were obtained from Danish KOL input (34). However, Knapp et al. is the source used in base case as the Danish KOL provided estimates for institutionalization much higher than any identified external sources. This was considered a conservative approach. Alternatively, a scenario analysis using the Danish KOL input was conducted.

To derive the institutionalization transition probabilities used in the model, the normalized probabilities of transition between the disease stages were multiplied by the probability of institutionalization specific to the state (Table 22) before the transition to obtain the complete transition probability matrix presented in Table 23 using NACC data.

Table 22 Transition Probabilities to Institutionalization

Scale	Institutionalization (per-cycle risk)
MCI due to AD	0.00%
Mild AD dementia	3.00%
Moderate AD dementia	8.00%
Severe AD dementia	10.00%

Note: Knapp et al. reports 6-months' probabilities which could be used directly in the calculation of the per-cycle risk.

Abbreviations: AD = Alzheimer's disease; MCI = mild cognitive impairment. Source: Knapp et al. (117)

Table 23 presents transition probabilities from the NACC analysis based on the CDR-SB matching the baseline patient age (73 years old) and percentage of females (55%) of the overall population in TB2. After rescaling to match the cycle length, the values in Table 23 represent the natural full transition probability matrix calculated for 6 months including institutionalization.

Table 23 Transitions in the health economic model

Health state (from)	Health state (to)	Description of method	Reference
MCI due to AD (community)	MCI due to AD (community) – 84.8%	**Community** A multinomial logistic regression model was fitted using maximum likelihood and was used to calculate the annual transition probabilities from one disease state to another disease state conditional on the initial state. The model controlled for time between visits (in days), continuous age (in years), and sex (male, female). The multinomial model produced a transition equation for each pair of consecutive visits, which related the predictors to the probability of transitioning to a given health state via the estimated model coefficients. The transition probability equations were then used to calculate mean transition probabilities for each pair (and associated 95% CIs) by holding constant age, sex, and time between visits (118). **Institutionalization** The normalized probabilities of transition between the disease stages derived from the sources presented above were multiplied by the probability of	Lilly, data on file, 2024 (118)
	Death – N/A*		
MCI due to AD (community)	Mild Dementia due to AD (community) - 14.3%		
	Death – N/A*		
MCI due to AD (community)	Moderate Dementia due to AD (community) - 0.7%		
	Death – N/A*		
MCI due to AD (community)	Severe Dementia due to AD (community) - 0.1%		
	Death – N/A*		
Mild Dementia due to AD (community)	Mild Dementia due to AD (community) - 79.4%		
	Death – N/A*		
Mild Dementia due to AD (community)	Moderate Dementia due to AD (community) - 16.1%		
	Death – N/A*		
Mild Dementia due to AD (community)	Severe Dementia due to AD (community) - 1.5%		
	Death – N/A*		

Mild Dementia due to AD (community)	Mild Dementia due to AD (institutionalized) – 2.5%	institutionalization specific to the state from Knapp et al. before the transition to obtain the complete transition probability matrix.
	Death – N/A*	
Mild Dementia due to AD (community)	Moderate Dementia due to AD (institutionalized) - 0.5%	
	Death – N/A*	
Mild Dementia due to AD (community)	Severe Dementia due to AD (institutionalized) - 0.0%	
	Death – N/A*	
Moderate Dementia due to AD (community)	Moderate Dementia due to AD (community) - 73.6%	
	Death – N/A*	
Moderate Dementia due to AD (community)	Severe Dementia due to AD (community) - 18.4%	
	Death – N/A*	
Moderate Dementia due to AD (community)	Moderate Dementia due to AD (institutionalized) - 6.4%	
	Death – N/A*	
Moderate Dementia due to AD (community)	Severe Dementia due to AD (institutionalized) – 1.6%	
	Death – N/A*	
Severe Dementia due to AD (community)	Severe Dementia due to AD (community) - 90.0%	
	Death – N/A*	
Severe Dementia due to AD (community)	Severe Dementia due to AD (institutionalized) - 10.0%	
	Death – N/A*	
MCI due to AD (institutionalized)	MCI due to AD (institutionalized) - 84.8%	

	Death – N/A*
MCI due to AD (institutionalized)	Mild Dementia due to AD (institutionalized) - 14.3%
	Death – N/A*
MCI due to AD (institutionalized)	Moderate Dementia due to AD (institutionalized) - 0.7%
	Death – N/A*
MCI due to AD (institutionalized)	Severe Dementia due to AD (institutionalized) - 0.1%
	Death – N/A*
Mild Dementia due to AD (institutionalized)	Mild Dementia due to AD (institutionalized) - 81.9%
	Death – N/A*
Mild Dementia due to AD (institutionalized)	Moderate Dementia due to AD (institutionalized) - 16.6%
	Death – N/A*
Mild Dementia due to AD (institutionalized)	Severe Dementia due to AD (institutionalized) - 1.5%
	Death – N/A*
Moderate Dementia due to AD (institutionalized)	Moderate Dementia due to AD (institutionalized) - 80.0%
	Death – N/A*
Moderate Dementia due to AD (institutionalized)	Severe Dementia due to AD (institutionalized) - 20.0%
	Death – N/A*
Severe Dementia due to AD (institutionalized)	Severe Dementia due to AD (institutionalized) - 100.0%
	Death – N/A*

*Death is dependent on both age and severity and therefore not a fixed proportion that can be reported in the above table. Further details on mortality are provided below.

Note: The probability of progression to a more severe disease stage displayed in the disease progression model sheet in the cost-effectiveness model does not account for the probability of dying and it is also broken down by residential status, hence the values don't exactly match the ones displayed in the table above.

Abbreviations: AD, Alzheimer's Disease; MCI, mild cognitive impairment; N/A, not applicable.

For clarity, the same data (Table 23) is also presented in Table 99 in Appendix R using a different layout.

Hazard ratio (HR) of disease progression for Donanemab versus BSC

The treatment effect was modeled as a decrease in the risk of a clinically meaningful worsening of symptoms, represented by a hazard ratio (HR) reducing the transition probabilities to worse states in the model. Clinically meaningful worsening (or MWPC) was defined as ≥1-point or ≥2-point worsening on CDR-SB for patients with MCI due to AD or mild AD, respectively at 2 consecutive visits. MCI due to AD was defined as an MMSE score of 27–30 at screening, while mild AD was defined as a score of 20–26. The difference between treatment arms in TB2 was estimated with a Cox proportional hazards model[9] resulting in an HR representing the reduction in risk of disease progression for patients treated with donanemab. The analysis was conducted using data from baseline to Week 76 from the EU eligible population, in a post-hoc analysis using the same methods as in a pre-specified but not herein reported analysis on the ITT population[10]. The HR was applied to natural history transition probabilities to more severe AD dementia states (see Table 24).

Table 24 Hazard Ratio of Disease Progression for Donanemab versus BSC (EU eligible population)

HR vs. BSC	MCI due to AD, Mild – Moderate AD Dementia	Severe AD Dementia
CDR-SB		
Donanemab	0.620 [95 % CI 0.49, 0.78]	N/A
Source	Lilly data on file, 2025: TB2 EU eligible population (119)	

Abbreviations: AD = Alzheimer's disease; CDR-SB = Clinical Dementia Rating Scale – Sum of Boxes; EU = European Union; HR = hazard ratio; MCI = mild cognitive impairment; TB2 = TRAILBLAZER-ALZ2

The findings in the EU eligible population are consistent with those observed for CDR-SB (38% lower risk of progression) in the overall studied population. The proportional hazard assumption of this model was investigated in the overall population; there was no evidence of violation of this assumption, the treatment effect was constant over time (see Appendix D). The possibility to use the risk of progressing a full stage based on CDR-SB thresholds per O'Bryant 2008 (HR of 0.708) was added in the model per DMC request (Disease Progression tab, row 61). This approach does not capture clinically meaningful

[9] See definition in Appendix TT

[9] See definition in Appendix TT

[10] See definition in Appendix TT

[10] The model was further stratified by pooled investigator sites and by the baseline tau category. The ties were handled using a discrete method.

deterioration *within* a health state and is heavily influenced by a patient's proximity to the boundary at baseline. By contrast, the MWPC definition (≥1-point change for MCI; ≥2-point for mild AD) measures each patient's individual trajectory of decline relative to their own starting point, capturing clinically relevant deterioration both *across* and *within* the full within-state severity spectrum. This approach therefore better reflects the clinical reality of AD as a continuum and is why MWPC was used to define the event in the base-case cost-effectiveness model.

Mortality

Background mortality was implemented by considering the age and gender mix in the cohort in the corresponding life tables. In the base case, country-specific age- and sex-adjusted general population mortality was applied, sourced from DMC addendum to the health economic model using published life tables for general population from DMC appendix (120). Given the prevalence of AD dementia among the older population, it is likely that the general population lifetables already capture the impact of AD dementia associated mortality. To avoid double counting, AD dementia-associated mortality was excluded from the lifetables for the base case. To exclude AD dementia mortality from the lifetables, the HR for AD dementia mortality and age-specific prevalence of AD dementia were used to derive the HR for mortality among patients with non-AD dementia. Specifically, excess mortality due to AD is removed from the lifetables as follows:

a. The mortality probabilities from general population lifetables are converted to an exponential rate (general population includes patients with and without AD).
b. For the estimations in the base case, the approach to adjust general population mortality to exclude AD-associated mortality was adopted from Ross et al. 2022 (121), a cost-effectiveness study for aducanumab and donanemab in AD dementia. The approach used a constant HR for mortality in patients with AD dementia (overall, regardless of disease severity) relative to the non-AD population.
c. In the model, AD prevalence was sourced from literature.
d. The relationship between general population mortality risk and mortality risk in AD dementia and non-AD dementia populations can be represented as follows:

$$Risk_{AD} = (HR_{AD\ vs\ non\ AD})Risk_{non\ AD}.$$

$$Risk_{gen\ pop} = (Prevalence_{AD})Risk_{AD} + (1 - Prevalence_{AD})Risk_{non\ AD}$$

The exponential rate of mortality converted from probabilities for non-AD dementia population was solved accordingly:

$$Risk_{non\ AD} = \frac{Risk_{gen\ pop}}{(1 - Prevalence_{AD} + (HR_{AD\ vs\ non\ AD})Prevalence_{AD})}$$

e. The exponential mortality risk for the non-AD dementia population was then converted back into mortality probabilities that could be used in the lifetables for the non-AD dementia population. The HRs for AD dementia specific mortality (discussed below) were applied to these derived lifetables.

AD and dementia are one of the leading causes of death, and the risk of dying is known to increase with severity. Therefore, the underlying risks of death from age and sex-

dependent life-table data were modified by the relative risk of deaths by disease stage. In the base case, these risk increments were informed by an analysis of data from NACC (118) (Table 25).

Table 25 Excess mortality due to AD dementia

AD dementia health state	Mean Hazard Ratio	95% Confidence Interval
MCI	1*	N/A
Mild AD	1.79	1.54, 2.09
Moderate AD	1.75	1.42, 2.14
Severe AD	3.41	2.87, 4.07

*No excess mortality is assumed in the MCI due to AD dementia health state
Abbreviations: AD, Alzheimer's disease; MCI, mild cognitive impairment. Source: Lilly data on file, 2024

Treatment-related mortality

In addition, the model provides the option of specifying treatment-related mortality for donanemab. This was applied as a one-time risk in the first cycle of the model. For donanemab, a risk of 0.63% was applied in the first cycle of the model based on a post-hoc analysis in the EU eligible patient population of TB6 trial (122). The mortality risk associated with donanemab was calculated using the total deaths considered related to treatment within the TRAILBLAZER-ALZ 6 trial divided by the total number of EU eligible trial participants. The resulting value was then converted into a percentage.

8.2 Presentation of efficacy data from [additional documentation]

Not applicable.

8.3 Modelling effects of subsequent treatments

Not applicable.

8.4 Other assumptions regarding efficacy in the model

Summary of evidence on continued treatment effect following treatment completion

As described in Section 6.1.4, using previously reported methods (Gueorguieva et al. 2023 (123), Shcherbinin et al. 2022 (112, 124)) and data from across studies I5T-MC-AACD, I5T-MC-AACG, I5T-MC-AACH (Parts B and C), AACI-PC, AACI Safety Addendum 9 (AACI-A9) and AACI-LTE, the estimated population median re-accumulation rate (95% CI) is 2.4 (2.2-2.6) CL/year (108). Findings that are supported by natural accumulation modelling studies (111). The impact of donanemab versus placebo on amyloid plaque deposition and its sustainability was therefore evaluated in TB2 by measuring changes in amyloid PET imaging from baseline to Week 76 (see result in Appendix B). Based on those observed amyloid levels at Week 76 in the EU eligible population and using a re-

accumulation rate of 2.4 CL per LTE study results (up to 2.5 years follow-up time post donanemab treatment completion, see Figure 34), the time taken for a return to an amyloid plaque level >24.1 CL, which equates to amyloid positivity, is more than 6 years, considering a continuous linear increase over time.

Published research supports that treatment effect is not lost when patients reach a threshold of ~24.1CL amyloid, with van der Kall et al. 2021 (125) reporting that patients with an amyloid plaque level of 26–50 CL at baseline showed little clinical progression until 4.5 years of follow-up (125, 126). Quenon et al. 2024 (126) reported in a study of 1,321 patients that an intermediate amyloid burden defined as 12–50 CL was not associated with an increased risk of clinical progression after 3.4 years (126). Additionally, Sperling et al (2024) reported that patients with an amyloid plaque level <46.1 CL showed minimal functional decline (127).

Assuming residual treatment effect at an amyloid plaque level >24.1 CL, it would take approximately 11 years to reach an amyloid level of 50 CL at a re-accumulation rate of 2.4 CL per year. It is worth noting that in TB2, the baseline amyloid plaque levels were 103.4 CL in the donanemab arm and 101.3 CL (128) in the placebo arm, which would require approximately 33 years of re-accumulation from 24.1 CL to reach this level of amyloid burden at a rate of 2.4 CL per year.

In addition, amyloid plaque clearance to levels that prevent the promotion of the spread of tau pathology, and therefore neurodegeneration, would provide a therapeutic benefit until the threshold is reached upon re-accumulation. Knopman et al. 2021 (129) analyzed the increase in tau PET flortaucipir signal in four regions of interest (entorhinal, inferior temporal, lateral parietal and a meta-region) in 167 cognitively normal participants who were allocated to four groups according to amyloid status: low, <–8 CL; subthreshold, 9–21 CL; suprathreshold, 22–67 CL; and high, >68 CL (129). They demonstrated that only in the >68 CL group was there a significant increase in annualized change in tau PET standardized uptake value ratio (SUVR), and that it is an increase in tau PET, rather than Aβ elevation, that is temporally linked to overt cognitive impairment. These results are consistent with the modelling simultaneously of Pittsburgh compound B (PIB) SUVR, flortaucipir SUVR, and cortical thickness, which showed that the decline in memory performance in patients who were cognitively normal occurred largely when Aβ levels exceeded 68 CL (130). The Aβ value of 68 CL or more, associated with flortaucipir accumulation, was in the range between MCI and dementia in a recent imaging-pathological study (131). Sperling et al. 2024 (127) also indicated that the degree of amyloid burden is the strongest predictor of functional decline. They demonstrated a dose-dependent impact of increasing CL burden on CDR-SB, with the greatest decline observed in patients with amyloid plaque levels of >77.2 CL.

Table 26 outlines the overall approach in the model.

Table 26 Summary of Approach to Long-term Treatment Effect within the Model

	TB2 population
Within trial	Full treatment effect is applied for the 18-month period whether treatment is completed early on confirmed amyloid clearance at either

	6 or 12 months or continued to the 18-month maximum without clearance, supported by CDR-SB 6- and 12-month completion data (Figure 8)
Post-trial: medium term	Full effect maintained for another 4.5 years based on the average time to return to an amyloid plaque level of 24.1 CL at an accumulation of 2.4 CL per year. This is calculated considering that: • Full treatment effect is retained for 4.5 years until patients have accumulated amyloid up to 'positive' level. • The mean amyloid level with the treatment of donanemab at 18-month is 12.67 CL. • 4.5 years are then calculated based on the above evidence [(24.1-12.67)/2.4≈4.8 years] Hence, the base case assumes that full treatment effect would then be retained throughout Year 6 (18-months [TB2] meaning 1.5 years plus ≈4.8 years).
Post-trial: long-term	Gradual waning over 11 years after the end of the full effect, assuming residual treatment effect at an amyloid plaque level >24.1 CL, with no treatment effect remaining at an amyloid plaque level of ~50 CL

Abbreviation: CL, Centiloids

Treatment completion and treatment effect assumptions

The treatment effect is simulated as an average cohort effect for all patients completing treatment at 24, 52 or 76 weeks (i.e. everyone except those with a negative stopping rule due to adverse events or reaching moderate stage). The treatment effect is based on the HR for the EU eligible population using data throughout the 18 months study. In the model, full treatment effect is applied for the 18-month period whether treatment is completed early on confirmed amyloid clearance at 6 or month 12 or continued to the 18-month maximum without clearance. Beyond these 18 months, full treatment effect was retained for an additional 4.5 years until patients have accumulated amyloid up to 'positive' level. Hence, the base case assumed that full treatment effect would then be retained for a total of 6 years, after which the treatment effect gradually wanes to zero.

The model provides flexibility to apply different assumptions around treatment effect waning and duration based on specific treatment completion scenarios (see Table 89 in Appendix L). These assumptions differ between patients who completed treatment due to positive stopping rules and those who discontinued due to negative stopping rules.

Positive stopping rules included:

- Treatment completion due to fixed treatment duration at 18 months; and/or
- Due to amyloid plaque clearance at 12 months; and/or
- Due to amyloid plague clearance at 6 and 12 months

Negative treatment stopping rules included:

- Discontinuation due to progression to moderate health state; and
- Discontinuation due to AEs

Positive stopping rule amyloid clearance versus 18 months treatment
The recommended approach is to initially limit the use of donanemab to selected Centers of Excellence that have access to amyloid-PET imaging. This offers an opportunity to optimize treatment by enabling precise monitoring at 6 and 12 months, or 12 months only, helping to ensure patients receive therapy for the most appropriate length of time. This proposal aligns with practices for other advanced treatments and is supported by several Danish KOLs (XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX).

In the model base case, all patients have access to a PET scan at 12 months, reflecting a response-guided, time-limited strategy. For comparison, two scenario analyses have been conducted, both presented in Section 12.2.:

1. A scenario in which 100% of patients receive PET scans at both 6 and 12 months.
2. A scenario without a response-guided, time-limited strategy, in which all patients are assumed to receive treatment for 18 months (unless discontinued for e.g. ARIAs), with 100% patients completing treatment at 18 months.

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

Table 28 presents modelled average treatment length and time in model health state. This information is seen as adequate to assess the differentiation of donanemab and no addition to BSC where the main source of efficacy extrapolation stems from the HR on CDR-SB scale from TB2 (presented in Table 24). Table 27 is therefore not populated.

Table 27 Estimates in the model

	Modelled average (reference in Excel)	Modelled median (reference in Excel)	Observed median from relevant study
Donanemab	N/A		
No addition to BSC			

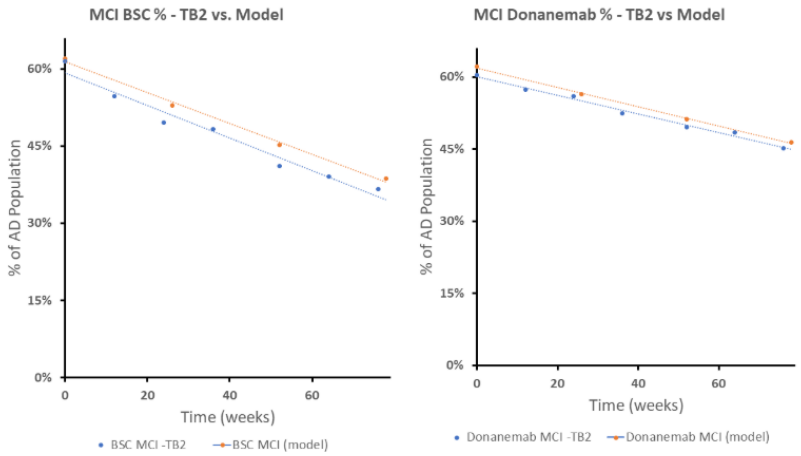
Table 28 Overview of modelled average treatment length and time in model health state, undiscounted and not adjusted for half cycle correction

Treatment	Treatment length [years]	MCI due to AD [years]	Mild AD [years]	Moderate AD [years]	Severe [years]	Death [years]
Donanemab	0.84	2.06	3.02	2.02	4.02	18.88
No addition to BSC	NA	1.43	2.25	1.80	5.14	19.38

Percentages from TRAILBLAZER-ALZ 2 overall population data and from the model for the overall TRAILBLAZER-ALZ2 population are provided below for each of the health states in the model. It is very important when interpreting these to recall that the model baseline distribution and relative treatment effect are based on the trial but that the model transition probabilities are based on the NACC data, not the trial; as such, it is not expected that the absolute model state occupancies will be aligned with those observed in the trial.

The model closely reproduces the trial based distribution of the MCI due to AD health state over time, for both BSC and donanemab. The model outputs show that slightly more patients remain in the MCI due to AD health state at 1.5 years (+2% BSC, +1% Donanemab) than the trial data indicates.

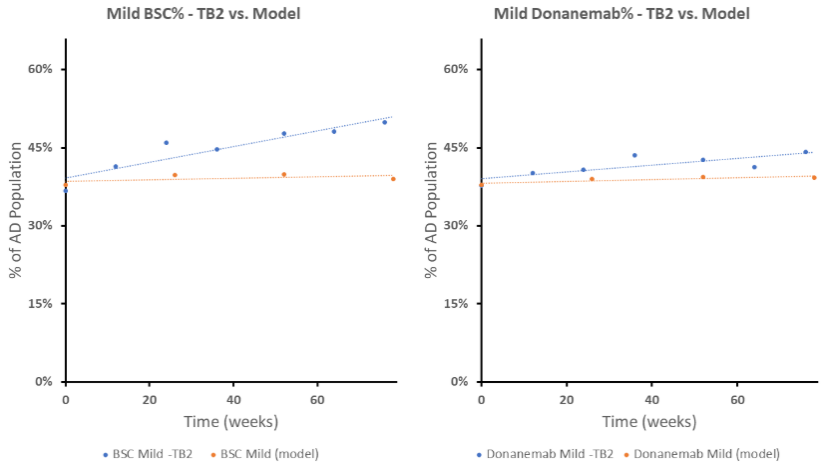
Figure 11 Comparison of the distribution of the MCI due to AD health state in the model and the TRAILBLAZER-ALZ 2 trial



Abbreviations: AD: Alzheimer's Disease; BSC: best supportive care; MCI: mild cognitive impairment; TB2: TRAILBLAZER-ALZ 2.

In the mild AD health state, patients can come from the MCI health state and move to the moderate health state. The model assigns at 18 months a smaller percentage of patients to the mild AD dementia health state for both BSC and donanemab (Figure 12) indicating that there are more movements in the model than in TB2 data and that the NAAC data for mild patients may result in slightly faster progression. The discrepancy between the model prediction and the trial data at 1.5 years is greater for BSC (−11%) than for donanemab (−5%).

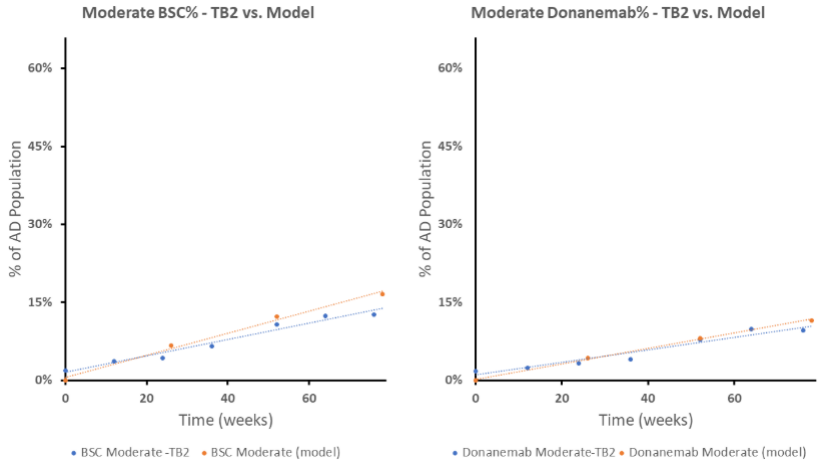
Figure 12 Comparison of the distribution of the mild AD dementia health state in the model and the TRAILBLAZER-ALZ 2 trial



Abbreviations: AD: Alzheimer's Disease; BSC: best supportive care; TB2: TRAILBLAZER-ALZ 2.

The model closely reproduces the trial based distribution of the moderate AD dementia health state over time, for BSC and donanemab (Figure 13). The discrepancy between the model prediction and the trial data at 1.5 years is greater for BSC (+4%) than for donanemab (+2%).

Figure 13 Comparison of the distribution of the moderate AD dementia health state in the model and the TRAILBLAZER-ALZ 2 trial

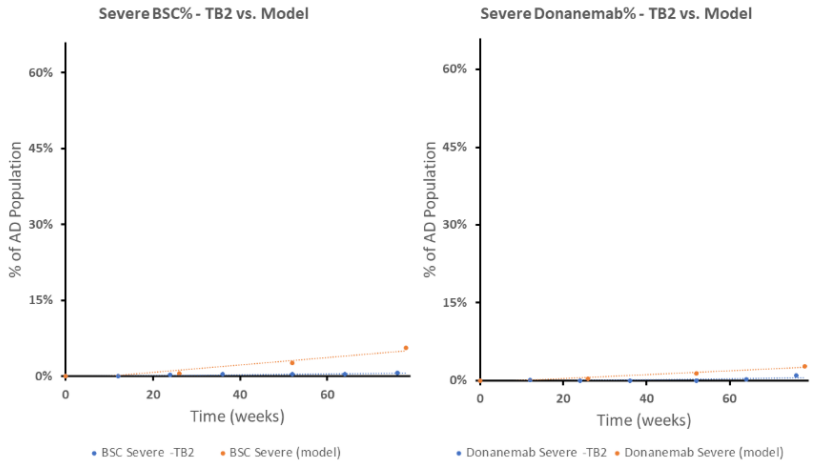


Abbreviations: AD: Alzheimer's Disease; BSC: best supportive care; TB2: TRAILBLAZER-ALZ 2.

The model assigns slightly more patients to the severe AD dementia health state than indicated by the trial data (Figure 14). The trial data does not show a clear difference between donanemab and BSC (based on very small sample sizes (6 patients in donanemab and 7 patients in BSC); however, the model indicates faster growth into the severe AD dementia health state for both donanemab and BSC. The discrepancy

between the model prediction and the trial data at 1.5 years is greater for BSC (+5.5%) than for donanemab (+2.5%). However, this needs to be interpreted with caution given the trial population (ie. early symptomatic AD), the trial design and relatively short timeframe (18 months) of the TRAILBLAZER-ALZ 2 trial, it was not possible to collect reliable long-term data in more severe health states.

Figure 14 Comparison of the distribution of the severe AD dementia health state in the model and the TRAILBLAZER-ALZ 2 trial



Abbreviations: AD: Alzheimer's Disease; BSC: best supportive care; TB2: TRAILBLAZER-ALZ 2.

Although broadly aligned, the differences observed in predicted state distribution of the BSC cohort (MCI / Mild / Moderate / Severe), over time, between the model and the TB2 trial, are reflective of differences between the NACC population and the trial population. The NACC population appears to progress slightly faster in the mild health state than the trial population, and the transition probabilities in the model are based on the NACC population. Because the NACC population progresses slightly faster than the TB2 population, the model assigns relatively more patients to the moderate and severe health states over the first 18 months than is seen in the TB2 trial, and relatively fewer patients to the mild health state.

We consider the NACC data set to be more reflective of a real-world context than the patients enrolled in the clinical trial. Real-world evidence is typically preferred over trial data to inform chronic disease progression, as it has a larger sample size and a longer follow up time. In the economic model, the clinical trial data have been used to establish the relative treatment effect as it is a randomised placebo-controlled phase III trial, while the NACC data set has been used to represent progression on best supportive care in the real-world population expected to benefit from the medicine. Based on Garcia et al. (132), Lilly found no evidence of treatment effect modifiers between the clinical trial population and NACC population, and therefore we consider it appropriate to apply the hazard ratio derived from the clinical trial to model the treatment effect.

9. Safety

9.1 Safety data from the clinical documentation

Safety data in line with TB2 (pivotal trial - Table 29) and TB6 (safety and modified dosing titration trial – Table 30) is presented below. For TB2, data is provided for both EU SmPC and EU eligible population, for TB6, data was only analyzed for EU eligible population.

Table 29 Overview of safety events in TRAILBLAZER-ALZ2 (data cut: 30 August 2024)

	EU SmPC (n=1438)			EU eligible (n=1212)		
	Donanemab (n=710)	Placebo (n=728)	Difference, % (95 % CI)	Donanemab (n=609)	Placebo (n=603)	Difference, % (95 % CI)
Number of adverse events, n	NR	NR	NR	NR	NR	NR
Number and proportion of patients with ≥1 adverse events, n (%)	NR	NR	NR	NR	NR	NR
Number of serious adverse events*, n	NR	NR	NR	NR	NR	NR
Number and proportion of patients with ≥ 1 serious adverse events*, n (%)	127 (17.9%)	111 (15.2%)	NR	89 (14.6)	74 (12.3)	NR
Number of CTCAE grade ≥ 3 events, n	NR	NR	NR	NR	NR	NR
Number and	NR	NR	NR	NR	NR	NR

	EU SmPC (n=1438)			EU eligible (n=1212)		
	Donanemab (n=710)	Placebo (n=728)	Difference, % (95 % CI)	Donanemab (n=609)	Placebo (n=603)	Difference, % (95 % CI)
proportion of patients with ≥ 1 CTCAE grade ≥ 3 events, n (%)						
Number of adverse reactions, n	NR	NR	NR	NR	NR	NR
Number and proportion of patients with ≥ 1 adverse reactions, n (%)	631 (88.9%)	592 (81.3%)	NR	533 (87.5)	481 (79.8)	NR
Number and proportion of patients who had a dose reduction, n (%)	NR	NR	NR	NR	NR	NR
Number and proportion of patients who discontinue treatment regardless of reason, n (%)	NR	NR	NR	NR	NR	NR
Number and proportion of patients who discontinue treatment due to	91 (12.8%)	28 (3.8%)	NR	73 (12.0)	22 (3.6)	NR

	EU SmPC (n=1438)			EU eligible (n=1212)		
	Donanemab (n=710)	Placebo (n=728)	Difference, % (95 % CI)	Donanemab (n=609)	Placebo (n=603)	Difference, % (95 % CI)
adverse events, n (%)						

Abbreviations: NR, not reported.

Table 30 Overview of safety events in TRAILBLAZER-ALZ6 (data cut: 3 April 2025)

	Donanemab EU eligible (n=158)
Non-severe*b ARIA-E and/or ARIA-H according to maximum radiographic severity AND who did NOT discontinue from Treatment due to an adverse event, n (%)	37 (23.42)
Moderate & severe IRR, n (%)	14 (8.86)
Moderate & severe hypersensitivity, n (%)	0
Anaphylactic reaction, n (%)	0
Discontinuation from Treatment due to an Adverse event OR severe ARIA-E and/or ARIA-H according to maximum radiographic severity, n (%)	14 (8.86)
Mean time to resolution for ARIA-E, days (SD)	61.9 (37.41)
Mortality risk (observed death), n (%)	1 (1)
% of non-carrier patients who experience an ARIA event prior to the 12th infusion, n (%)	15/68 (22.10)
% of heterozygote patients in EU eligible patient population requiring a 12th MRI, n (%)	NR (59.49)

* Overall AACI/AACQ population excluding APOE E4-E4 patients, excluding patients with missing APOE status, excluding anticoagulants, and patients with uncontrolled hypertension (defined as AND)

Abbreviations: ARIA-E, Amyloid-related imaging abnormality – oedema/effusion; ARIA-H, Amyloid-related imaging abnormality – microhaemorrhages and haemosiderin deposits; IRR, Infusion Related Reaction; MRI, magnetic resonance imaging; NR, not reported; SD, standard deviation. Sources: Lilly Data on File TFLs on safety TRAILBLAZER-ALZ 6. 2025

Table 31 presents most important serious adverse events.

Table 31 Serious adverse events

	EU SmPC (n=1438)				EU eligible (n=1212)			
Adverse events	**Donanemab (N=710)**		**Placebo (N=728)**		**Donanemab (N=609)**		**Placebo (N=603)**	
	Number of patients with adverse events	**Number of adverse events**	**Number of patients with adverse events**	**Number of adverse events**	**Number of patients with adverse events**	**Number of adverse events**	**Number of patients with adverse events**	**Number of adverse events**
ARIA-E (%)	9 (1.3%)	NR	NR	NR	6 (1.0%)	NR	0 (0.0%)	0 (0.0%)
ARIA-H (%)	2 (0.3%)	NR	NR	NR	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Hypersensitivity including IRR (%)	3 (0.4%)	NR	NR	NR	1 (0.2%)	NR	0 (0.0%)	0 (0.0%)
Anaphylactic reactions (%)	3 (0.4%)	NR	NR	NR	3 (0.5%)	NR	0 (0.0%)	0 (0.0%)

In Table 32 below, the adverse events included in the health economic model are presented. Amyloid-related imaging abnormalities with edema/effusion (ARIA-E) or ARIA with hemorrhages (ARIA-H) events have been observed after treatment with donanemab and are therefore important AEs for consideration with this treatment. As such, all-grade events for ARIA were considered in the health economic model. For other treatment-related AEs, Infusion-related reactions (IRRs), and hypersensitivity, moderate and severe events were included and all anaphylaxis cases. According to the EU SmPC for donanemab, treatment with donanemab should be permanently discontinued in the event of radiographically or symptomatic severe ARIA-E or ARIA-H (73).

AEs were not considered for the BSC arm in the model, although ARIA-E/H were observed in the placebo arm in both TRAILBLAZER-ALZ (133) and TB2 (5), given that there are AEs associated with BSC. In the model, more weight was therefore placed on the AEs for the donanemab treatment arm than observed across trials, making this approach conservative. All AE events for donanemab were informed using the TB6 trial data in the EU eligible population. The incidence of AEs included in the model for patients receiving donanemab are reported in Table 32. The mean time to ARIA-E resolution in the EU eligible population in TB6 was 61.9 days. The EU SmPC for donanemab highlights that a follow-up MRI to assess for resolution (ARIA E) or stabilization (ARIA H) should be performed 2 to 4 months after initial identification. Conservatively though, the model

assumes that for ARIA, two ad-hoc MRIs are being conducted until it either stabilizes or resolves.

Table 32 Adverse events used in the health economic model

Adverse events	Donanemab	No addition to BSC		
	Frequency used in economic model for intervention	Frequency used in economic model for comparator	Source	Justification
Adverse event, n (%)				
Non-Severe ARIA Event - Trial Reported Incidence	NR (23.42%)	-	Eli Lilly data on file	Incidence Rate of All-Grade ARIA Events and Serious AEs (Grade 3+) over Trial Period.
Non-Severe ARIA Event - % of Events that Are Symptomatic	NR (11.54%)	-		
IRR^	NR (8.86%)			
Hypersensitivity^	NR (0.0%*)	-		
Anaphylactic Reaction	NR (0.0%*)	-		

^Only moderate and severe cases are considered. * No case was reported in TRAILBLAZER-ALZ 6 for the EU eligible population. Abbreviations: AE, Adverse Event; ARIA, amyloid-related imaging abnormalities; IRR, infusion-related reaction.

As most ARIA events occur within the first 3–6 months of treatment initiation, the rate of non-severe ARIA events observed from the trial was applied during the first cycle (6 months) in the model (134). The rates for moderate or severe IRR and hypersensitivity as well as anaphylactic reaction (all grades) were informed by TB6 and were converted to 6-month probabilities aligned with the model cycle length and used in the model calculations.

In clinical practice, patients may stop treatment due to ARIA events and severe ARIA events, anaphylaxis, IRRs or hypersensitivity. Discontinuation due to AEs and severe ARIA was implemented using discontinuation due to AE and severe ARIA cases (8.86%) (74) for the EU eligible population in TB6.

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

Not applicable.

Table 33 Adverse events that appear in more than X % of patients

Adverse events	Intervention (N=x)			Comparator (N=x)			Difference, % (95 % CI)	
	Number of patients with adverse events	Number of adverse events	Frequency used in economic model for intervention	Number of patients with adverse events	Number of adverse events	Frequency used in economic model for comparator	Number of patients with adverse events	Number of adverse events
Adverse event, n	Not applicable.							

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

EQ-5D data were not collected in the TB2 trial as it was not considered sufficiently sensitive to detect treatment differences in early AD population. Data on QoL-AD (a disease specific instrument) were collected in a subset of patients and given the 18 months trial duration, data did not reflect the entire AD disease spectrum. Therefore, the data was not considered relevant for this health economic assessment and an economic SLR was performed (see Section 5.2) to identify the most relevant source for HRQoL and other economic aspects for the population included in the health economic model. More information on the data included is presented in Section 10.3. The full SLR report is available on request.

Table 34 Overview of included HRQoL instruments

Measuring instrument	Source	Utilization
EQ-5D	Landeiro et al. (2020)	The EQ-5D instrument was used to calculate the utility values reported (by caregivers) in a SLR and fixed-effect meta-analysis performed by Landeiro et al. and which informed the patient utilities in the model.
Time trade-off	Matza 2024 (135)	Only in scenario analysis
Time trade-off	Belger et al. (2022) (136)	Only in scenario analysis

10.1 Presentation of the health-related quality of life

10.1.1 Study design and measuring instrument

HRQoL data were collected using the Quality of Life in Alzheimer's Disease (QoL-AD) questionnaire in a subset of the total TRAILBLAZER-ALZ 2 population (Addendum 4, n=767). Addendum 4 refers to a protocol amendment introduced when the study was expanded from a Phase IIb to a Phase III trial; a dedicated statistical analysis plan was developed at that time, so these endpoints are considered prespecified but non-gated (i.e. not part of the primary multiplicity testing scheme).

The baseline characteristics of the Addendum 4 population were consistent with the overall study population. Both patient-assessed (subject) and care partner-assessed (proxy) versions of the QoL-AD were administered at Weeks 24, 52, and 76. The QoL-AD covers 13 items rated on a 4-point scale, with a total score range of 13–52, where higher scores indicate better HRQoL.

10.1.2 Data collection

Table 35 Pattern of missing data and completion

Time point	HRQoL population N	Missing N (%)	Expected to complete N	Completion N (%)
	Number of patients at randomization	Number of patients for whom data is missing (% of patients at randomization)	Number of patients "at risk" at time point X	Number of patients who completed (% of patients expected to complete)
N/A				

10.1.3 HRQoL results

Table 36 HRQoL [instrument 1] summary statistics

	Intervention		Comparator		Intervention vs. comparator
	N	Mean (SE)	N	Mean (SE)	Difference (95% CI) p-value
N/A					

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

No mapping algorithm was used to derive patient quality-of-life (QoL) values. EQ-5D was not collected in TRAILBLAZER-ALZ2, and the QoL-AD instrument was collected only in a subset of patients and, over the 18-month trial duration, did not reflect the entire AD disease spectrum, as described in Section 10.

Furthermore, we are not aware of the existence of a validated mapping function from QoL-AD to EQ-5D by AD disease severity stage; a severity-specific mapping was therefore not available to convert the trial QoL-AD data into utilities. Therefore, patient health-state utility values were sourced directly from a published meta-analysis by AD dementia severity stage (Landeiro et al. 2020) and then age-adjusted to match the TRAILBLAZER-ALZ2 population, with continued age adjustment as the model progresses (per the NICE Decision Support Unit recommendation, Hernández Alava et al. Utility values were applied by health state and were assumed not to differ by setting (community vs residential care).

The patient utility values are EQ-5D ratings of patient HRQoL provided by carers, reported by AD dementia severity stage (Landeiro et al. 2020). This proxy-rated approach was used because assessing the QoL of patients with AD dementia across the full disease spectrum is challenging, and a meta-analysis of EQ-5D estimates gave more robust, less uncertain values than any single study or the QoL-AD data from TRAILBLAZER-ALZ2 could have provided. The utility values decrease with disease severity.

Caregiver utilities were included to reflect the societal perspective and the documented burden of AD dementia on care partners. They were not derived from EQ-5D: recent research indicated that the EQ-5D lacks sensitivity across the AD severity range, and so was not considered an appropriate measure of caregiver impact. Caregiver utility values were therefore derived from two vignette studies using a time trade-off (TTO) approach (Matza 2024 for the community setting and MCI/mild states; Belger 2022 for severe/institutionalized states) – as recommended by NICE for situations in which use of EQ-5D is not appropriate. Caregiver utilities were modeled by patient AD severity stage, by setting (community/institution), and separately for child and spouse caregivers.

This section is therefore considered not applicable.

10.2.1 HSUV calculation

Not applicable.

10.2.1.1 Mapping

Not applicable.

10.2.2 Disutility calculation

Not applicable.

10.2.3 HSUV results

Table 37 Overview of health state utility values [and disutilities]

	Results [95% CI]	Instrument	Tariff (value set) used	Comments
N/A				

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

The systematic literature review on QoL studies (research question 2, more details in Appendix I) to support this application focused on observational studies, including prospective and retrospective cohort studies, vignette studies and cross-sectional surveys as outlined in the corresponding protocol. Therefore, the Landeiro paper was not identified since it reports the findings of a systematic literature review and subsequently

a meta-analysis of QoL information reported in experimental studies, quasi-experimental studies, prospective or retrospective observational studies and registry-based studies reporting quality of life information across the Alzheimer Disease stages. Similar to our search, other systematic literature reviews or evidence synthesis were not in scope. The Landeiro paper however was identified as part of the economic model search (research question 1, more details in Appendix I), which aimed to understand the existing models in terms of structure, strengths and weaknesses but also key inputs to parameterize the models. The full SLR report is available on request.

10.3.1 Study design

Patient utility values were sourced from Landeiro et al. (8)- a meta-analysis of disease stage specific utilities that provided a more robust level of evidence and reduced uncertainty around the point estimates compared to a single study. The study was developed based on a comprehensive literature review of EQ-5D estimates of health-state utilities. For more details about caregivers' utilities see Appendix F.

10.3.2 Data collection

Data from Landeiro et al. 2020 (8) was collected through a systematic literature review of studies published between 1990 and 2017 that reported health-related quality of life in people with pre-dementia Alzheimer's disease, mild cognitive impairment, or dementia. The authors searched multiple databases following PRISMA guidelines and included studies using preference-based instruments capable of generating utility values, mainly the EQ-5D. Data was extracted on study characteristics, respondent type, disease severity, and reported utilities, which were then summarized and meta-analysed by disease stage and respondent. For more details about caregivers' utilities see Appendix F.

10.3.3 HRQoL Results

Not reported.

10.3.4 HSUV and disutility results

Table 38 Overview of health state utility values [and disutilities]

	Results [SD]	Instrument	Tariff (value set) used	Comments
Not applicable				

Table 39 shows average utility values carer-reported in Landeiro et al. 2020 (8) that were used in the model. As these utilities were obtained from a population different from the TB2 trial, the utilities were adjusted to match the characteristics in terms of age of the TB2 trial, correcting for differences between the trial and the utility data source. To do this, the utilities were multiplied by an adjustment factor created by accounting for how

the general population utilities change based on age, so that the final utilities used in the model are estimated for a population with the same age composition as in the trial and are continually adjusted for age as the model progresses.

The information button in the 'Utility' tab in the section which is titled Health State Utilities provides the following explanation. All starting health state utilities are adjusted from the input literature source so that they better match the age and sex characteristics of the trial population, according to the standard multiplicative methods described in the NICE health technology evaluations manual.

Disutility values associated with AEs were applied in the model. Disutility for all symptomatic non-severe ARIA events was applied for the average duration of such events as a one-time utility decrement. Since headache was the most reported symptom among patients with symptomatic ARIA, the disutility value for a headache (–0.14), obtained from Xu et al. 2011 (137) was used as a proxy for ARIA disutilities. No anaphylactic reactions or infusion-related hypersensitivity reaction was observed in the EU eligible population in TB6. For moderate to severe infusion-related reactions, no utility decrement was applied as in clinical practice, patients would be effectively treated for these AEs (as per expert physician opinion) and the cost of treating infusion related reactions are included within the model. Additionally, only moderate, and severe IRRs events were considered as mild cases would be managed by slowing down the rate of infusion. Disutility values for AEs were sourced from published literature and are presented in Table 39.

In the model base case, caregivers' utility values were excluded. The inclusion of caregivers' utility values based on Belger et al. (2022) (136) and Matza et al (2024) (135) is explored in a scenario analysis (see Appendix F for a description on the data collection and chosen health state utility values).

Table 39 Overview of literature-based health state utility values

	Results [SE]	Instrument	Tariff (value set) used	Comments
Patients's HSUV				
MCI due to AD - community and institutionalised	0.813 [0.08]	EQ-5D	-	Patients with MCI due to AD are assumed to reflect the general Danish population utility (patient is 70 years old in line with Danish KOL input).
Mild AD Dementia - community and institutionalised	0.74 [0.03]	EQ-5D	Various value sets	
Moderate AD Dementia -	0.59 [0.06]	EQ-5D	Various value sets	Community and institutionalised: Landeiro et al. 2020 (8)

	Results [SE]	Instrument	Tariff (value set) used	Comments
community and institutionalised				Since Landeiro et al. 2020 is a meta-analysis including data from multiple countries and value sets and because Lilly does not have access to the individual patient data from the original trials, it was not possible to calculate utility values using the Danish preference weights.
Severe AD Dementia - community and institutionalised	0.36 [0.08]	EQ-5D	Various value sets	

Disutilities	Disutility	Duration (Days)	
ARIA events	-0.14	61.9 days	Disutility: Xu et al. 2011 (137) Duration: Lilly data on file (75)
Anaphylactic reaction	-0.116	30 days	Hannouf 2012 (138); 15% reduction in utility applied to baseline utility (weighted average of MCI and mild AD based on initial distribution).

Abbreviations: AD dementia, Alzheimer's disease; ARIA, amyloid-related imaging abnormalities; MCI, mild cognitive impairment.

11. Resource use and associated costs

Healthcare resource use and cost inputs were based on clinical trial data and published literature as well as standard publicly available databases. Inflation adjustments were applied for any costs prior to 2025, using the average consumer prices index excluding energy for 2025.

11.1 Medicines - intervention and comparator

To accurately estimate drug costs, the model considered the appropriate treatment duration lengths, mode of administration, dosing intervals, titration, and discontinuation as per the EMA label and clinical practice.

There is no wastage assumed in the model as this is not a weight-based treatment.

Table 40 Medicines used in the model

Medicine	Dose	Relative dose intensity	Frequency	Vial sharing
Donanemab	Dose 1: 350 mg, Dose 2: 700 mg, Dose 3: 1,050 mg, Dose 4 and onward: 1,400 mg.	97.28%	every four weeks	No
BSC	Donepezil: 10 mg Memantine: 20 mg	100%	Once daily	No

Abbreviation: BSC, best supportive care.

Note: The RDI is intended to represent the ratio between the dose effectively administered and the target dose. An overall RDI of 97.28% was applied for donanemab, calculated as a weighted average based on the following inputs: the proportion of patients for whom treatment was interrupted due to non-severe ARIA cases (23.42%) (74), the mean duration of treatment interruption as observed from the EU eligible patient population in TB6 trial (61.9 days, or about two doses) (75), and the TB6 treatment duration (18 months or 19 x 28-day dosing cycles) (134).

11.2 Medicines– co-administration

Costs of background therapy (i.e., concomitant medications, such as acetylcholinesterase inhibitors [AChEIs]) were included in the model. The annual cost of each medication, and the proportion of patients who receive each medication by AD dementia stage, are specified in Table 41. The acquisition costs are based on the pharmacy purchasing price (PPP/AIP) and they were retrieved from Medicinpriser.dk (139). As multiple strengths and pack sizes were available for several of the treatments which are part of the best supportive care, the prices sourced in the model correspond to the cheapest price per mg (among all available strengths and pack sizes). The cost of AChEIs in Table 41 is based on the cost of donepezil as being the most used AChEI in Danish clinical practice according to Danish KOL (34).

Table 41 Costs and Distribution for Concomitant Medications

Medication	Annual Cost	Proportion of Patients Who Receive the Medication by AD Stage (%)				Source
		MCI due to AD	Mild AD Dementia	Moderate AD Dementia	Severe AD Dementia	
Acetylcholinesterase inhibitor	DKK 176.73	0%	80%	70%	65%	Based on price on donepezil as per KOL insights, Donepezil Jubilant (v.nr 149057)
Memantine	DKK 425.00	0%	2%	20%	25%	Memantin "Accord" (v.nr 132155)

Patients receive daily dose over entire year. Abbreviations: AD, Alzheimer's disease; MCI, mild cognitive impairment. Note: In clinical practice, patients can use more than one drug at the same time, therefore the

sum of drug distribution exceeds 100% based on expert opinion. However, the percentages are adjusted for the model so they sum to 100%.

11.3 Administration costs

Donanemab is administered via IV infusion, which is associated with administration costs. The administration costs considered within the model are summarized in Table 42.

Duration of treatment administration was based on 30 minutes of treatment administration followed by 30 minutes of observation, based on the TB2 trial (5). For the base case, costs were derived from Sundhedsdatastyrelsen 2026 DRG tariffs (140).

Table 42 Administration costs used in the model

Administration type	Frequency	Unit cost [DKK]	DRG code	Reference
Donanemab: Infusion 1st hour[a]	every 4th week	2,061	01MA98	DRG takster 2026
Donanemab: Infusion subsequent hours	every 4th week	0	Assumption: DRG code 01MA98 includes the whole time needed for infusion	-
Established clinical management	-	No administration costs were included in the model for BSC	-	-

[a]Assumes 30 minutes administration followed by 30 minutes observation based on the TRAILBLAZER-ALZ2 protocol. Abbreviations: BSC, best supportive care; Q4W, every 4 weeks

11.4 Disease management costs

Resource utilization costs by AD dementia severity and setting (community/institutionalised care) were specified in the model. In the context of a limited societal perspective in line with DMC guidelines, direct medical plus patient social care and residential care costs were taken into consideration in the base case. Direct medical care costs include inpatient care, outpatient care (encompassing specialist as well as primary care, visits to nurses and other healthcare professionals) and pharmaceuticals. Patient social care costs include all other non-medical care services such as home help, day care and delivered meals, while residential care costs include nursing home, group living or other institution. Given the particularity of the disease burden, the last two categories of costs (patient social care costs and residential care costs) were deemed to be relevant to be included alongside the direct medical costs in the base case. As a scenario analysis, a societal perspective was explored, in which to the

the above-mentioned costs (direct medical costs, patient social care and residential care costs), direct non-medical care costs (i.e., caregiver informal care costs) were also included in the analysis.

Most costs in AD dementia are expected to increase with severity as the patient's burden increases although this may not occur in a linear pattern. In order to inform costs per AD dementia stage, cost inputs were identified from published literature and inflated to 2025 values by applying the average consumer price index excluding energy, which was sourced from Statistics Denmark (141).

Table 43 presents the stage-specific costs considered in the base case. These were calculated as the sum of the direct medical costs, patient social care costs and residential care costs. All the stage-specific costs in the analysis are based on Jönsson et al. 2022 (142). For MCI stage costs, given the fact that a cost for MCI stage was not available in Jönsson et al. publication, the MCI costs in both community and institutionalised setting was assumed to be equal to 56% based on Sköldunger et al. 2013 (143) of the Mild AD Dementia cost from Jönsson et al. 2022 (142). The costs were converted to DKK and inflated to 2025 as described previously.

Table 43 Annual Direct Costs (Base Case)

Health states	Total costs	
Community		
MCI due to AD	DKK	70,685
Mild AD dementia	DKK	126,224
Moderate AD dementia	DKK	117,663
Severe AD dementia	DKK	110,866
Institutionalised Care		
MCI due to AD	DKK	357,114
Mild AD dementia	DKK	637,704
Moderate AD dementia	DKK	523,823
Severe AD dementia	DKK	524,825

Abbreviations: AD, Alzheimer's disease; HRU, health resource utilization; MCI, mild cognitive impairment

The costs for caregiver informal care costs (included only in a societal perspective scenario) were also retrieved from Jönsson et al. 2022 (142) and the same principle for the MCI stage cost applies as described above.

Table 44 shows a sum of all direct and indirect annual costs included in the model. In line with the findings from Jönsson et al. 2022 (142), it is possible to observe that the total annual costs increase with disease progression in the community setting.

Table 44 Total annual costs

	Community				Institutionalized			
	MCI due to AD	Mild AD Dementia	Moderate AD Dementia	Severe AD Dementia	MCI due to AD	Mild AD Dementia	Moderate AD Dementia	Severe AD Dementia
Annual direct costs (included in the base case analysis)								
Direct medical costs (medication, hospitalization)	DKK 22,245	DKK 39,724	DKK 37,860	DKK 40,438	DKK 12,264	DKK 21,899	DKK 25,969	DKK 25,273
Patient Social Care Costs	DKK 39,879	DKK 71,213	DKK 77,889	DKK 70,428	DKK 330	DKK 589	DKK 497	DKK 807
Residential care costs	DKK 8,561	DKK 15,287	DKK 1,884	DKK -	DKK 344,521	DKK 615,216	DKK 497,357	DKK 498,745
Total direct costs	DKK 70,685	DKK 126,224	DKK 117,633	DKK 110,866	DKK 357,114	DKK 637,704	DKK 523,823	DKK 524,825
Annual indirect costs (included only in scenario analysis)								
Caregiver *Informal Care Costs*	DKK 45,994	DKK 82,131	DKK 119,180	DKK 158,074	DKK 0	DKK 0	DKK 0	DKK 0
Total annual costs								
Sum of direct and indirect costs	DKK 116,679	DKK 208,355	DKK 236,813	DKK 268,940	DKK 357,114	DKK 637,704	DKK 523,823	DKK 524,825

Furthermore, costs associated with diagnostic testing, amyloid monitoring, AEs monitoring, and monitoring consultations were applied in the model. Regarding diagnostic testing, it was assumed a 1.13 number of MRI and 1.18 number of APOE ε4 tests performed per patient in accordance with the assumption on the DMC assessment of another amyloid-targeting therapy (53). This higher than unity assumption takes into consideration that more patients need to be tested than those identified as eligible for treatment, and that these tests are typically not conducted in BSC today. The unit costs of each resource category were taken from the Sundhedsdatastyrelsen 2026 DRG tariffs (140) and Rigshospitalets Labportal (144) and are summarized in Table 45.

Table 45 Disease management costs used in the model

Activity	Frequency	Unit cost [DKK]	DRG code	Reference
MRI scan	1.13 MRIs per patient	2,638.00	30PR02	DRG 2026
Amyloid PET scan	1 PET scan at 12 months	4,681.00	36PR06	DRG 2026
APOE ε4 Test	1.18 tests per patient	3,112.00	31PR03	DRG 2026

Abbreviations: APOE, apolipoprotein CSF, cerebrospinal fluid; MRI, magnetic resonance imaging; PET, positron emission tomography

Amyloid Monitoring Costs

In the model base case, 100% of patients are tested using amyloid-PET scan in line with Danish clinical expert inputs (16, 17) and thus reflecting a response-guided, time-limited strategy. Scenario analyses were conducted where amyloid-PET scans are used at both 6 and 12 months, and where PET cannot be adopted (i.e. 0% of patients screened for amyloid clearance). The costs of monitoring amyloid positivity during treatment were based on costs for an amyloid-PET scan. Unit costs for amyloid monitoring resources are summarized in Table 45.

Monitoring Consultation Costs

The base case included the costs for disease monitoring consultations. According to a Danish KOL in specialty care, MCI patients will have the same number of specialty-care visits after diagnosis regardless of whether or not they start donanemab, because MCI patients are routinely followed (biannually) in specialty-care until they reach the mild AD stage and become eligible for cholinesterase-inhibitors. Consequently, both the MCI patients in the BSC-arm and donanemab-arm will have biannual visits in specialty care, and thus no biannual monitoring costs for donanemab patients have been applied to MCI patients in the model.

For mild AD patients, according to a Danish KOL, all patients after diagnosis whether or not they start donanemab will have a follow-up visit (count as the first bi-annual visit), but thereafter all donanemab patients would have one additional annual monitoring visit and just 15% of the BSC patients would have one annual monitoring visit (BSC patients will be routinely followed after diagnosis in specialty care if considered fragile). The model therefore has one annual visit for all donanemab patients and for 15% BSC

patients. The cost of the visit was 2,061 DKK (DRG: 01MA98 "MDC01 1-dagsgruppe, pat. mindst 7 år"). The patient time and transportation costs incurred are described in Section 11.7.

11.5 Costs associated with management of adverse events

The incidence of AEs (ARIA events and moderate to severe IRRs) is discussed in Section 9.1. Monitoring costs for AEs, specifically ARIA, were applied as a one-time cost in the first model cycle and were based on the total frequency of MRI scans for ARIA event monitoring over the trial period specified. As per the EMA label, it was assumed that patients would receive four regular MRI scans during the follow-up period and patients with an increased ARIA risk (i.e. APOE4 heterozygotes and APOE4 non-carrier patients with an ARIA event prior to the 12th infusion) would receive an additional MRI scan prior to the 12th infusion (i.e., 5 MRI scans in total).

In addition, the cost of two additional ad hoc MRI scans was assumed when an ARIA event occurred. This is a conservative assumption as in practice, it is likely just one MRI may be required per patient. Unit costs for MRI scans were sourced from Sundhedsdatastyrelsen 2026 DRG tariffs (140).

The costs of treating AEs (Table 46) were multiplied by the probabilities of each event to derive the total cost for each treatment. ARIA event costs (including MRI scan costs) were calculated as a 6-month period cost to align with the model cycle length and were applied in the first model cycle (6 months) to align with the occurrence of ARIA events described in Section 9.1. Moderate and severe IRR costs were calculated as 6-month period costs to align with the model cycle length and were applied for the duration of the trial period, adjusting for the proportion of each model cycle (6 months).

Table 46 Cost associated with management of adverse events

	DRG code	Unit cost/DRG tariff
ARIA-E and ARIA-H	Cost for ARIA events are based on 2 MRIs (30PR02 "MR-scanning, kompliceret" [DKK 2,638]) plus a specialist visit (01MA98 "MDC01 1-dagsgruppe, pat. mindst 7 år" [DKK 2,061]).	DKK 7,337
Infusion Related Reactions	One week of treatment with levocetirizine "PharmaCoDane" with the price/pill of 0.8206 DKK	DKK 5.74

Abbreviations: ARIA = amyloid-related imaging abnormalities; MRI = magnetic resonance imaging

11.6 Subsequent treatment costs

Not applicable.

Table 47 Medicines of subsequent treatments

Medicine	Dose	Relative dose intensity	Frequency	Vial sharing
Not applicable				

11.7 Patient costs

As per DMC guidelines (145), the costs incurred by patients and their families as a consequence of the medicine treatment (transport costs and time spent) must be included in the health economic model. The value of time for patients and their families is recommended to be calculated at a common rate, regardless of employment situation, and assigned the value of leisure time. In the model, the value of leisure time was retrieved from DMC's Supplementary guidelines (146), based on the average gross hourly salary in Denmark, based on Statistics Denmark, which is 200 DKK per hour. The costs of transportation for a round trip were sourced from the same source and amounted to 150 DKK.

The patient time and transportation cost is based on a combination of the average hourly wage (200 DKK), estimated time spent in connection to treatment (1.5 hours) and the cost of transportation for a round trip (150 DKK). In the model, only 50% of the patients were assumed to be accompanied by their care partners during their treatment. These calculations are outlined in the 'Resource Utilization Costs' sheet, cells P89:P95. Table 48 presents the costs incurred as a consequence of the medicine treatment (and respective time estimations).

Table 48 Patient and caregiver costs used in the model in connection with treatment visits

Activity	Time spent [minutes, hours, days]
Estimated time spent in connection to treatment (waiting time and IV administration)	1.5 hours for patients (conservative estimate on the SmPC estimation of 1 Hour) Total patient cost: DKK 450
Estimated time spent for care partners in connection with treatment of a patient (transportation and waiting time)	Based on DMC assumption in another amyloid-targeting therapy assessment, 50% of patients are bringing a care partner, thus care partner time in total is 0.75 hours (1.5 * 0.5 = 0.75) Total care partner cost: DKK 150

In addition to patient time in connection with receiving treatment, two other aspects were included in the base case analysis:

- Costs for patient time in connection with MRI scans (both scheduled scans and those linked to the investigation of ARIA events): It was assumed that the time spent on an MRI scan was 40 minutes (20 minutes for preparation + 20 minutes

for the scan) based on Danish KOL input (using an hourly rate of 200 DKK/h). It was assumed there was no coordination of the MRI scan with the visit to receive treatment if the treatment is implemented today, based on Danish KOL opinion. However, the KOL was supportive of a future multidisciplinary approach that could lead to patients having coordinated visits for MRI and treatment infusions. Hence a scenario analysis is presented where 100% coordination is assumed. Similarly to the visits to receive treatment, it was assumed that 50% of patients would be accompanied by a caregiver. Transportation cost was also included (150 DKK) and assumed to be the same if the caregiver would join (patient and caregiver would travel together). The total patient cost per MRI visit was 283.40 DKK and the total caregiver cost per MRI visit was 141.70 DKK.

- Costs for patient time in connection with annual monitoring visit: It was assumed that all patients in the donanemab arm and 15% of patients in the BSC arm would incur one annual monitoring visit, based on Danish KOL input. The visit was assumed to take 30 minutes, also based on Danish KOL input (using an hourly rate of 200 DKK/h). Transportation cost was also included (150 DKK). The total cost for a monitoring consultation was 2,311 DKK (which includes also the specialist visit described in Section 11.4).

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

Not applicable.

12. Results

12.1 Base case overview

An overview of the base case is presented in Table 49.

Table 49 Base case overview

Feature	Description
Comparator	BSC
Type of model	Markov model
Time horizon	30 years (life time)
Treatment line	1st line. Subsequent treatment lines are not included.
Measurement and valuation of health effects	Health-related quality of life measured with EQ-5D from Landeiro et al.
Costs included	Medicine costs

Feature	Description	
	Administration costs	
	Disease managements costs	
	Costs of monitoring adverse events	
	Patient and caregiver costs	
	Terminal care costs	
Dosage of medicine	Based on weight	
Average time on treatment	Donanemab: 0.84 years	
	No addition to BSC: 10.62 years	
Inclusion of waste	No vial sharing	
Average time in model health state (discounted values)	Donanemab	No addition to BSC
Community setting	6.86 years	6.08 years
MCI due to AD	1.86 years	1.32 years
Mild AD	2.65 years	2.03 years
Moderate AD	1.24 years	1.22 years
Severe AD	1.13 years	1.50 years
Institutionalized setting	2.15 years	2.62 years
MCI due to AD	-	-
Mild AD Dementia	-	-
Moderate AD Dementia	0.40 years	0.32 years
Severe AD Dementia	1.75 years	2.30 years

12.1.1 Base case results

Table 50 Base case results, discounted estimates

	Donanemab	No addition to BSC	Difference
Acquisition Costs	DKK 248,621	DKK -	DKK 248,621
Administration and Related Costs	DKK 26,092	DKK -	DKK 26,092
Diagnostic Testing Costs	DKK 6,653	DKK -	DKK 6,653
Amyloid Monitoring Detection Costs	DKK 3,644	DKK -	DKK 3,644

	Donanemab	No addition to BSC	Difference
ARIA Adverse Events Costs	DKK 13,945	DKK -	DKK 13,945
Non-ARIA Adverse Events Costs	DKK 0	DKK -	DKK 0
Disease Management Costs	DKK 1,869,074	DKK 2,032,669	DKK 163,595
Concomitant Medication Costs	DKK 667	DKK 685	DKK 18
Terminal Care Costs	DKK -	DKK -	DKK -
Patient Time and Transportation Costs	DKK 7,596	DKK -	DKK 7,596
Total costs	**DKK 2,176,291.91**	**DKK 2,033,353.40**	**DKK 142,938.51**
Community setting	6.86	6.08	0.78
MCI due to AD	1.86	1.32	0.54
Mild AD	2.65	2.03	0.62
Moderate AD	1.24	1.22	-0.02
Severe AD	1.13	1.50	-0.37
Institutionalized Setting	2.15	2.62	-0.47
MCI due to AD	-	-	-
Mild AD	-	-	-
Moderate AD	0.40	0.32	0.08
Severe AD	1.75	2.30	-0.55
Total life years	**9.02**	**8.69**	**0.33**
Community setting	4.60	3.84	0.76
MCI due to AD	1.51	1.08	0.43
Mild AD	1.96	1.50	0.45
Moderate AD	0.73	0.72	0.01
Severe AD	0.41	0.54	- 0.14

	Donanemab	No addition to BSC	Difference
Institutionalized Setting	0.87	1.01	- 0.15
MCI due to AD	-	-	-
Mild AD	-	-	-
Moderate AD	0.24	0.19	0.05
Severe AD	0.63	0.83	- 0.20
Utility Decrement Due to Adverse Events	0.00	-	0.00
Total QALYs	**5.47**	**4.85**	**0.61**
Incremental costs per life year gained		**437,580**	
Incremental cost per QALY gained (ICER)		**232,912**	

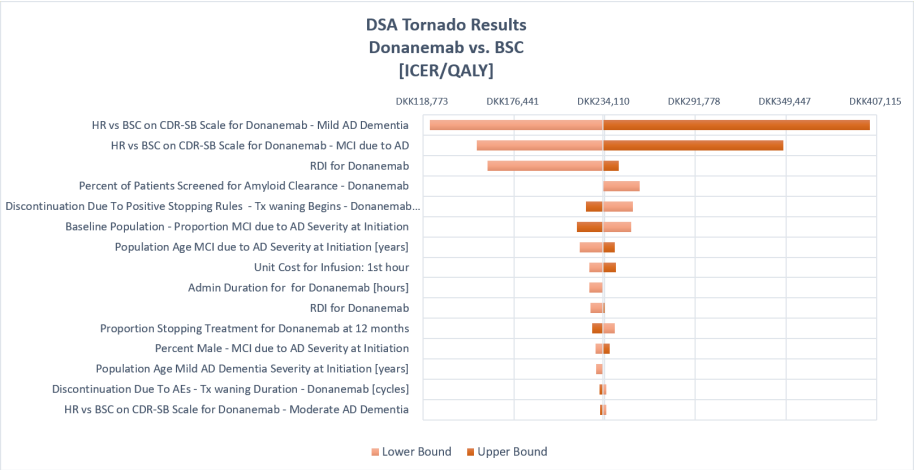
12.2 Sensitivity analyses

Uncertainty in the model parameters was assessed in deterministic sensitivity analyses, scenario analyses and probabilistic sensitivity analyses.

12.2.1 Deterministic sensitivity analyses

All major model variables in the base case that were subject to uncertainty were tested in a one-way deterministic sensitivity analysis to identify model drivers and understand the impact of uncertainty in specific model parameters. Where possible, confidence intervals (CI), or published ranges were used as alternative values. In the absence of CIs or published ranges, lower and upper bounds tested in the one-way sensitivity analysis were calculated as ± 20% of the mean value. The 15 most influential parameters on the ICER/QALY, ranked by their level of impact, are presented in the tornado diagram in Figure 15.

Figure 15 One-way Sensitivity Analysis



Abbreviations: AD, Alzheimer's disease; BSC, best supportive care; CDR-SB, Clinical Dementia Rating Scale – Sum of Boxes; DSA, deterministic sensitivity analysis; HR, hazard ratio; ICER, incremental cost-effectiveness ratio; MCI, mild cognitive disorder; QALY, quality-adjusted life year; RDI, relative dose intensity

In addition, relevant scenario (one parameter changed per scenario) analyses are presented in Table 51. In the model base case, 100% of patients have access to a PET scan at 12 months, thus reflecting a limited dosing strategy. [redacted] Scenario analyses were conducted where patients can complete treatment at 6 months and 12 months (which decreased the ICER by 31%), and where PET scans cannot be adopted (0% of patients screened for amyloid clearance, which increased the ICER by 50%).

Table 51 One-way sensitivity analyses results

	Change (DKK)	Reason / Rational / Source	Incremental cost (DKK)	Incremental benefit (QALYs)	ICER (DKK/QALY)
Base case					232,912
Perspective	Societal	To test the impact of adding caregiver informal care costs	-	-	[redacted]
Time horizon	5 years	Show scenarios on shorter horizons	-	-	[redacted]
	10 years		-	-	[redacted]
	20 years		-	-	[redacted]
Discount rate	Costs/effects: 0%	Test undiscounted	-	-	[redacted]

	Change (DKK)	Reason / Rational / Source	Incremental cost (DKK)	Incremental benefit (QALYs)	ICER (DKK/QALY)
	Costs/effects: 5%	and with a higher discount rate	-	-	XXXXXXX
Initial Population - MCI	21%	Test impact on proportion of MCI patients in line with TB2	-	-	XXXXXXX
	70%	Test impact on proportion of MCI patients in line with Leqembi decison	-	-	XXXXXXX
Institutional care costs	No	Provide a scenario where community setting is used	-	-	XXXXXXX
Perspective & Institutional care costs	Societal & No	-	-	-	XXXXXXX
Treatment complete due to Amyloid Clearance	6-month and 12-month	Provide a scenario where patients can complete treatment at 6 months and 12 months instead of at 12 months only	-	-	159,686
Proportion of patients screened for amyloid clearance	0%	Test the impact of not having	-	-	350,294

	Change (DKK)	Reason / Rational / Source	Incremental cost (DKK)	Incremental benefit (QALYs)	ICER (DKK/QALY)
		access to PET scan			
Risk of institutionalization by disease stage	Source: Danish KOL	Provide a scenario with local inputs	-	-	XXXXXXX
Transition probabilities	Source: Potashman et al. 2021	Provide an alternative source	-	-	XXXXXXX
Caregiver utility	Included Source: Matza et al 2024 and Belger et al. 2022	Provide a scenario with caregiver utility included	-	-	145,119
Proportion of patients needing separate MRI Trip	0%	Provide a scenario in which all patients have coordinated visits.	-	-	XXXXXXX

12.2.2 Probabilistic sensitivity analyses

The model performs probabilistic analysis, and reports mean outcomes (and 95% CIs) for all outputs. For the probabilistic results, uncertainties in parameter values were estimated including clinical inputs, costs, and utility values. Measurement of uncertainties was captured by 95% CIs or Standard Error (SE) for each parameter. In the absence of CIs or SEs from published sources, the SE for the parameter was assumed to be 10% of the mean value.

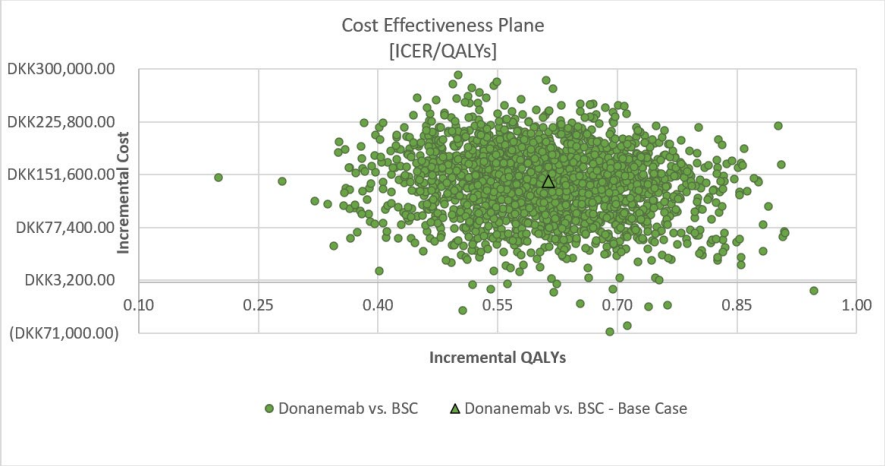
After processing all the iterations, the model generated a scatter plot illustrating the distribution of incremental costs and incremental QALYs from the probabilistic results, as well as cost-effectiveness acceptability curves depicting the likelihood of donanemab being cost-effective relative to a comparator over a range of willingness-to-pay thresholds per QALY.

The appropriate number of iterations for probabilistic analysis was assessed based on convergence tests. Convergence tests reviewed if the variance around probabilistic model outputs (ICER or net monetary benefit) stabilizes as the number of iterations is increased and determined if more iterations are required based on this. The probabilistic analysis is run for a relatively large number of iterations (e.g., 1,000 to 5,000), and the

cumulative mean for different outcomes is evaluated repeatedly and represented graphically relative to the number of iterations. The optimal number of iterations is such that there is no clear trend in the cumulative average as the number of iterations grows and that the cumulative average does not have substantial jumps (which would be indicative of some random samples still having a substantial impact on the average outcome). This is because the influence of each random sample is reduced as the number of samples (iterations) increases, effectively reducing Monte Carlo error. The probabilistic analysis was performed with 2,000 iterations. The probabilistic results are presented below.

The total health outcomes (in QALYs) were plotted against the total cost of donanemab and BSC on the cost-effectiveness plane (Figure 16) to present the variation in incremental QALYs and ICER over 2,000 replications comparing donanemab versus BSC.

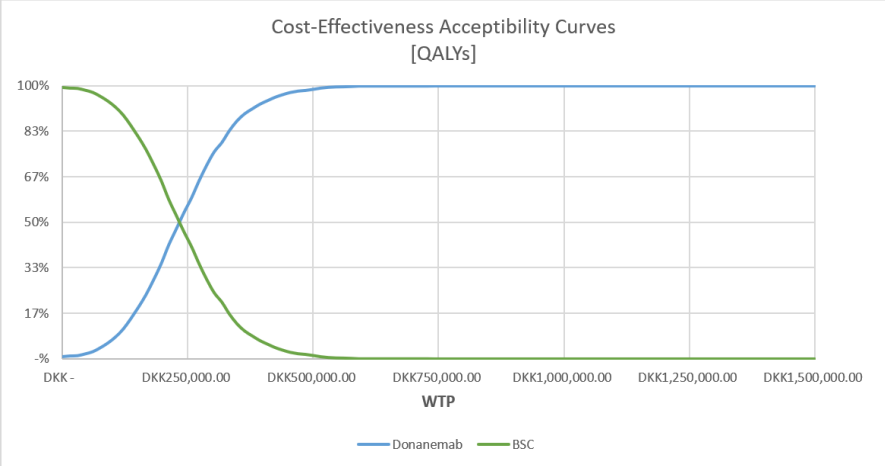
Figure 16 Cost-effectiveness plane



Abbreviations: ICER, Incremental Cost-Effectiveness Ratio; QALYs, Quality-adjusted life-years

The cost-effectiveness acceptability curve indicates that donanemab had a 50% probability of being cost-effective at a willingness-to-pay of approximately DKK 240 thousand (Figure 17).

Figure 17 Cost-effectiveness acceptability curve



Abbreviations: QALYs, Quality-adjusted life-years; WTP, Willingness to pay

13. Budget impact analysis

Number of patients [redacted]

Patient Flow

The patient flow starts with prevalent patients with MCI or mild dementia due to AD who are amyloid positive in year 1. After that, a new cohort of incident patients enters the model in each subsequent year (up to 4 years). After year 5, no new cohort enters the model but the patients entering the model during years 1 to 5 continue till the end of the selected time horizon. Within the time horizon, disease progression and on/off donanemab are tracked based on treatment-specific inputs. In the BIM, the number of patients eligible for donanemab is derived based on the patient funnel in line with a previous DMC assessment of another ATT (53)

[redacted]

In another ATT assessment by DMC (published 17. Dec 2025) (53), DMC assumes 650 patients per year will be treated with the ATT. Thus, this serves as the foundation for estimating eligible patients for donanemab.

[redacted]

In the base case, for the reference market without donanemab, 100% of market share is assigned to BSC. In the new scenario (with donanemab), the projected market uptake of donanemab is assumed [redacted] Considering that all patients in the model undergo an amyloid-PET scan at 12 months and may complete treatment if cleared for amyloid plaque, this impacts the number of patients in year 2 onwards. Therefore, the cumulative numbers, summing up the new patients entering treatment every year with those remaining on treatment for 18 months (69.7% complete treatment at 12 months)

[redacted] The market shares and the number of new patients entering treatment every year with donanemab is presented in Table 52. The model has an option for the user to enter direct market share input for both reference and scenarios.

Table 52 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		
Donanemab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BSC only	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
			Non-recommendation		
Donanemab	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
BSC only	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviation: BSC, best supportive care.

Budget impact

The BIM is an analogue of the CEM (i.e. the functionality of the CEM is leveraged to produce all costing for the BIM). The costs input from the BIM are derived from section 11 along with the disease progression. These cost outputs from the CEM engine were then mapped onto the patient numbers and the time horizon in the BIM to calculate the total costs. The costs are disaggregated into the same categories as reported in the CEM.

Table 53 Expected budget impact of recommending the medicine for the indication

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

A scenario analysis including 50% more patients was conducted to address any uncertainty on the number of eligible patients estimate, with results shown in Table 54.

Table 54 Scenario analysis of budget impact, numbers adjusted to address any uncertainty on the number of eligible patients estimates

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

14. List of experts

[redacted]

15. References

Note: Lilly data on file references are available upon request.

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Appendix A. Main characteristics of studies included

The main characteristics of the studies included in this application alongside the ones part of the clinical trial program are summarized in Table 55.

Table 55 Main characteristics of studies included

Trial name: TRAILBLAZER-ALZ2	**NCT number: NCT04437511**
Objective	The TRAILBLAZER-ALZ 2 trial aimed to confirm and expand upon the results from TRAILBLAZER-ALZ by assessing the efficacy and adverse events of donanemab in a larger and more diverse group of participants.
Publications – title, author, journal, year	Sims JR, Zimmer JA, Evans CD, Lu M, Ardayfio P, Sparks J, et al. Donanemab in Early Symptomatic Alzheimer Disease: The TRAILBLAZER-ALZ 2 Randomized Clinical Trial. Jama. 2023;330(6):512-27.
Study type and design	Multicentre, randomised, double-blind, placebo-controlled, 18-month, phase III trial (Completed).
Sample size (n)	*1736 participants,* EU SmPC 1447 patients, EU eligible 1218 patients
Main inclusion criteria	Diagnosis of early symptomatic AD (mild cognitive impairment or mild dementia), presence of brain amyloid, low-medium or high tau levels (as confirmed by PET scan).
Main exclusion criteria	Central reading of MRI scan undertaken during the screening period showed presence of: ARIA-E, ≥4 cerebral microhemorrhages, more than 1 area of superficial siderosis, any intracerebral hemorrhage >1 cm, severe white matter disease.
Intervention	Donanemab (n=873), induced with 700 mg 3x Q4W, followed by maintenance with 1400 mg Q4W up to 72 weeks. EU SmPC n=717 patients and EU eligible n=614 patients.
Comparator(s)	Placebo (n=880), induced with 700 mg 3x Q4W, followed by maintenance with 1400 mg Q4W up to 72 weeks. EU SmPC n=730 and EU eligible n=604.
Follow-up time	up to 44 weeks.
Is the study used in the health economic model?	Yes, this is the pivotal trial.

Trial name: TRAILBLAZER-ALZ2	NCT number: NCT04437511
Primary, secondary and exploratory endpoints	Primary: • Change from BL in iADRS (NCS2) at W76 Secondary: • Change from BL in CDR-SB (MMRM) at W76 • Change from BL in ADCS-Cog13 (NCS2) at W76 • Change from BL in ADCS-iADL (NCS2) at W76 • Change from BL in MMSE at W76 (NCS2) • Change from BL in amyloid at W76, CL (MMRM) • Proportion of participants with amyloid clearance at W24 (Fisher's exact test) • Proportion of participants with amyloid clearance at W76 (Fisher's exact test) • Change from BL in tau frontal SUVR to W76 (ANCOVA) • Change from BL in vMRI measures (MMRM) Exploratory • Time to disease progression – iADRS Time-PMRM at W76 • Time to disease progression – CDR-SB Time-PMRM at W76 • Time to clinical worsening – CDR-G TTE (Cox proportional hazards model) • Disease progression MWPC – iADRS (Cox proportional hazards model) • Disease progression MWPC – iADRS (Cox proportional hazards model) • Non-progression at 1 year – CDR-SB at W52 (GLMM) • Change from BL in plasma P-tau217 to W24 (MMRM) • Change from BL in plasma P-tau217 to W76 (MMRM) • Change from baseline to W76 in GFAP and NfL (MMRM) **Endpoints included in this application:** The study included several endpoints. However, only results of the key study endpoints: change from BL in iADRS (NCS2) at W76 – primary endpoint and change from BL in CDR-SB (MMRM) at W76 – secondary endpoint are presented in this submission (in Section 6.1.4). Furthermore, the efficacy results used in the health economic analysis are the change from baseline in CDR-SB. The results for the other endpoints are therefore not presented here. **Other endpoints:**

Trial name: TRAILBLAZER-ALZ2	NCT number: NCT04437511
	The results for the other endpoints are therefore not presented, as these are not considered relevant to this submission.
Method of analysis	Efficacy analyses were conducted using the evaluable efficacy population (i.e. the overall population, also referred to as the modified intention-to-treat [mITT]), which included all participants with a baseline and ≥1 post-baseline efficacy measurement based on randomised treatment (5). A Time-Progression Model for Repeated Measures was used to analyze slowing of disease progression at Week 76 as measured by the iADRS and CDR-SB (non-gated in the overall population). The percentage slowing relative to placebo was calculated using the NCS2 model for the iADRS and the MMRM for the CDR-SB. The hazard ratio (HR) of progressing to meaningful clinical worsening between treatment groups was estimated using a Cox proportional hazard model, with a clinical worsening event defined as a CDR-G increase from baseline at two consecutive visits (a gated endpoint), and a decrease from baseline in the iADRS and increase from baseline in the CDR-SB.
Subgroup analyses	Several subgroup analyses were conducted for TRAILBLAZER-ALZ2 to support the primary and key secondary efficacy measures. Analyses included those by baseline demographic groups (e.g. age, sex, race, and BMI) and by groups of specific interest in AD (e.g. APOE ε4 status, symptomatic medication use, and clinical staging at baseline). The following information was not reported: - characteristics of included population - method of analysis - was it pre-specified or post hoc? - assessment of validity, including statistical power for pre-specified analyses.
Other relevant information	*N/A.*

Abbreviations: ADAS-Cog13, Alzheimer's Disease Assessment Scale – 13-item Cognitive subscale; ADCS-iADL, Alzheimer's Disease Cooperative Study – instrumental Activities of Daily Living subscale; BL, baseline; CDR-G, Clinical Dementia Rating Scale – Global score; CDR-SB, Clinical Dementia Rating Scale – Sum of Boxes; CL, centiloid; GFAP, glial fibrillary acidic protein; GLMM, generalised linear mixed model; iADRS, integrated Alzheimer's Disease Rating Scale; MMRM, mixed models for repeated measures; MMSE, mini mental state examination; MWPC, meaningful within person change; NCS2, natural cubic spline model with 2 degrees of freedom; NfL, neurofilament light chain; PMRM, progression model for repeated measures; SUVR, standard uptake value ratio; TTE, time-to-event; W, week.

Trial name: TRAILBLAZER-ALZ2 LTE	NCT number: NCT04437511
Objective	The long-term extension (LTE) of TRAILBLAZER-ALZ2 assessed clinical efficacy and safety of treatment with donanemab over an additional 78-week treatment period that followed the 76-week main study period.
Publications – title, author, journal, year	Zimmer JA, Sims JR, Evans CD, Nery ESM, Wang H, Wessels AM, et al. Donanemab in early symptomatic Alzheimer's disease: results from the TRAILBLAZER-ALZ 2 long-term extension. The Journal of Prevention of Alzheimer's Disease. 2025:100446.
Study type and design	Multicentre, randomised, double-blind, 78 weeks, long-term extension of TB2 phase III trial (Completed).
Sample size (n)	*1207 participants.* EU SmPC and EU eligible were not reported
Main inclusion criteria	Participants who were included in TRAILBLAZER-ALZ2.
Main exclusion criteria	Participants who met the dose cessation criteria by 76 weeks of the TB2.
Intervention	Donanemab (n=814), maintenance with 1400 mg Q4W up to 78 weeks (W154 in total). EU SmPC and EU eligible were not reported
Comparator(s)	Control cohort derived from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database over a 3 year period used to compared clinical changes assessed by the CDR-SB.
Follow-up time	up to 78 weeks.
Is the study used in the health economic model?	Yes, this is the long-term extension of the pivotal trial.
Primary, secondary and exploratory endpoints	• CDR-SB change from baseline with ADNI matched controls at W78 (W154 in total) • Early start versus delayed start in donanemab treatment: impact on the risk of progression on CDR-G score at W78 (W154 in total) • Biomarker endpoints at W78 (W154 in total) Endpoints included in this application: The study included several endpoints. However, only results of the key study endpoints: change from BL in iADRS (NCS2) at W76 – primary endpoint and change from BL in CDR-SB (MMRM) at W76 – secondary endpoint are presented in this submission (in Section 6.1.4). Furthermore, the efficacy results used in the health economic analysis are the change from baseline in CDR-SB. The results for the other

Trial name: TRAILBLAZER-ALZ2 LTE		NCT number: NCT04437511
	endpoints are therefore not presented here, as these are not considered relevant to this submission. Other endpoints: The results for the other endpoints are therefore not presented, as these are not considered relevant to this submission.	
Method of analysis	Efficacy analyses were conducted using the evaluable efficacy population (also referred to as the modified intention-to-treat [mITT]), which included all participants with a baseline and ≥1 post-baseline efficacy measurement based on randomised treatment (5). A Time-Progression Model for Repeated Measures was used to analyse slowing of disease progression at Week 76 as measured by the iADRS and CDR-SB (non-gated in the overall population). The percentage slowing relative to placebo was calculated using the NCS2 model for the iADRS and the MMRM for the CDR-SB. The hazard ratio (HR) of progressing to meaningful clinical worsening between treatment groups was estimated using a Cox proportional hazard model, with a clinical worsening event defined as a CDR-G increase from baseline at two consecutive visits (a gated endpoint), and a decrease from baseline in the iADRS and increase from baseline in the CDR-SB.	
Subgroup analyses	Several subgroup analyses were conducted for TRAILBLAZER-ALZ2 to support the primary and key secondary efficacy measures. Analyses included those by baseline demographic groups (e.g. age, sex, race, and BMI) and by groups of specific interest in AD (e.g. APOE ε4 status, symptomatic medication use, and clinical staging at baseline). The following information was not reported: - characteristics of included population - method of analysis - was it pre-specified or post hoc? - assessment of validity, including statistical power for pre-specified analyses.	
Other relevant information	*N/A.*	

Abbreviations: ADNI, Alzheimer's Disease Neuroimaging Initiative; CDR-SB, Clinical Dementia Rating Scale – Sum of Boxes; iADRS, integrated Alzheimer's Disease Rating Scale; MMRM, mixed models for repeated measures; NCS2, natural cubic spline model with 2 degrees of freedom; W, week.

Trial name: TRAILBLAZER-ALZ 6		NCT number: NCT05738486
Objective	This study was conducted as part of continued efforts to reduce the risk of ARIA, and investigated the effect of different donanemab dosing	

Trial name: TRAILBLAZER-ALZ 6	NCT number: NCT05738486
	regimens on ARIA and amyloid lowering in adults with early symptomatic AD.
Publications – title, author, journal, year	Wang H, Serap Monkul Nery E, Ardayfio P, et al. Modified titration of donanemab reduces ARIA risk and maintains amyloid reduction. Alzheimer's Dement 2025a;21:e70062.
Study type and design	Multicentre, randomised, double-blind, phase IIIb, parallel group, 4-arm study (Completed).
Sample size (n)	*843 participants*
Main inclusion criteria	• Eligible study participants were men or women aged 60–85 years of age inclusive with: ○ Gradual and progressive change in memory function for ≥6 months from providing informed consent. ○ A MMSE score of 20–28 (inclusive) at Visit 1. ○ An amyloid PET scan result showing presence of amyloid pathology.
Main exclusion criteria	• Have significant neurological disease affecting the central nervous system other than AD, that may affect cognition or ability to complete the study, including but not limited to, other dementias, serious infection of the brain, Parkinson's disease, multiple concussions, or epilepsy or recurrent seizures, except febrile childhood seizures. • Has current serious or unstable illnesses including cardiovascular, hepatic, renal, gastroenterologic, respiratory, endocrinologic, neurologic (other than AD), psychiatric, immunologic, or hematologic disease and other conditions that, in the investigator's opinion, could interfere with the analyses in this study. • A life expectancy of <24 months • Have a presence or history of malignant neoplasms within the past 5 years prior to Visit 1.
Intervention	Donanemab dose level 1 (standard) n=208: three doses of 700 mg every 4 weeks, followed by 1400 mg every 4 weeks thereafter. Donanemab dose level 2 (modified titration) n=212: 350 mg as the first dose, then 700 mg as the second dose after 4 weeks, then 1050 mg as the third dose after another 4 weeks, followed by 1400 every 4 weeks thereafter. Donanemab dose level 3 (dose skipping) n=210: 700 mg as the first dose, followed by 1400 mg at week 8, and then 1400 mg every 4 weeks thereafter. Donanemab dose level 4 (maximum observed drug concentration) n=213: six doses of 350 mg every 2 weeks, then two

Trial name: TRAILBLAZER-ALZ 6	NCT number: NCT05738486
	doses of 700 mg every 2 weeks, followed by 1400 mg every 4 weeks thereafter.
Comparator(s)	Placebo
Follow-up time	91 weeks
Is the study used in the health economic model?	Yes, TRAILBLAZER-ALZ6 data is used for the dosing regimens in the integrated safety analysis which in turn is used as the source for the safety data used in the model. No other data are used from this study.
Primary, secondary and exploratory endpoints	Primary: • Proportion of participants with any occurrence of ARIA-E by Week 24, given the alternative donanemab dosing regimens versus the standard dosing regimen (7) Secondary: • Proportion of participants with any occurrence of ARIA-E by Week 52. • Change from baseline in brain amyloid plaque deposition (PET) at Weeks 24, 52, and 76. • Proportion of participants with any occurrence of ARIA-H at Weeks 24 and 52. • ARIA-E and ARIA-H severity.
Method of analysis	A Bayesian logistic regression model which included fixed effects for treatment regimen, apolipoprotein E ε 4 status, baseline presence of microhemorrhage, baseline presence of cortical superficial siderosis, and baseline amyloid level, was used to evaluate the relative reduction in ARIA frequencies through week 76 for each alternative dosing arm compared to the standard dosing arm. The prespecified success criterion was a posterior probability of more than 80 % that at least 1 alternative dosing arm reduced ARIA risk (RRR) by at least 20 % compared to the standard arm by 24 weeks. ARIA severity was assessed with the Cochran-Mantel-Haenszel test. The effect of each alternative donanemab dosing regimen compared with the standard donanemab dosing regimen on brain amyloid deposition, plasma P-tau217, and plasma GFAP through 76 weeks was assessed using a mixed model for repeated measures (MMRM) with fixed effects for treatment, visit, treatment-by-visit interaction, baseline value, base- line value-by-visit interaction, and baseline age with an unstructured variance–covariance.
Subgroup analyses	NR
Other relevant information	*N/A*

Abbreviations: AD, Alzheimer's Disease; ARIA, Amyloid-related imaging abnormality; ARIA-E, Amyloid-related imaging abnormality – oedema/effusions; ARIA-H, Amyloid-related imaging abnormality – microhaemorrhage/ haemosiderin deposits; MMRM, mixed models for repeated measures; PET, Positron emission tomography.

Trial name: TRAILBLAZER-ALZ	**NCT number: NCT03367403**
Objective	The objective of the TRAILBLAZER-ALZ trial was to evaluate the safety, adverse events, and efficacy of donanemab in patients with early symptomatic Alzheimer's disease.
Publications – title, author, journal, year	Mintun MA, Lo AC, Duggan Evans C, Wessels AM, Ardayfio PA, Andersen SW, et al. Donanemab in Early Alzheimer's Disease. N Engl J Med. 2021;384(18):1691-704.
Study type and design	Multicentre, randomised, double-blind, placebo-controlled, 18-month, phase II trial (Completed).
Sample size (n)	*257 participants*
Main inclusion criteria	Age 60-85 years, diagnosis of prodromal AD or mild AD with dementia, MMSE score of 20-28, and amyloid pathology confirmed by PET scan.
Main exclusion criteria	Central reading of MRI scan undertaken during the screening period showed presence of ARIA-E, ≥4 cerebral microhemorrhages, more than 1 area of superficial siderosis, any intracerebral hemorrhage >1 cm, severe white matter disease.
Intervention	Donanemab (n=131), induced with 700 mg 3x Q4W, followed by maintenance with 1400 mg Q4W up to 72 weeks.
Comparator(s)	Placebo (n=126) matched to the dosing schedule of the intervention group.
Follow-up time	48 weeks.
Is the study used in the health economic model?	Yes, TRAILBLAZER-ALZ data is used in the integrated safety analysis which in turn is used as the source for the safety data used in the model. No other data are used from this study.
Primary, secondary and exploratory endpoints	Primary: • Change in iADRS score from BL to W76 Secondary (MMRM): • Change from BL to W76 in CDR-SB, ADAS-Cog13, ADCS-iADL, MMSE, amyloid plaque levels, brain tau levels, and vMRI measures. **Endpoints included in this application:** The efficacy results used in the health economic analysis will be informed by the change from baseline in CDR-SB. **Other endpoints:**

Trial name: TRAILBLAZER-ALZ	NCT number: NCT03367403
	The results for the other endpoints are therefore not presented, as these are not considered relevant to this submission.
Method of analysis	Efficacy analyses were conducted on the ITT population, which included all participants who had a baseline and ≥1 post-baseline iADRS score (133). The primary endpoint was analysed using MMRM, with the change from baseline in iADRS score at each scheduled post-baseline time point as the dependent variable. Secondary efficacy endpoints were also assessed using MMRM.
Subgroup analyses	Not deemed relevant to include
Other relevant information	*N/A*

Abbreviations: ADAS-Cog13, Alzheimer's Disease Assessment Scale – 13-item Cognitive subscale; ADCS-iADL, Alzheimer's Disease Cooperative Study – instrumental Activities of Daily Living subscale; BL, baseline; CDR-G, Clinical Dementia Rating Scale – Global score; CDR-SB, Clinical Dementia Rating Scale – Sum of Boxes; CL, centiloid; GFAP, glial fibrillary acidic protein; iADRS, integrated Alzheimer's Disease Rating Scale; MMRM, mixed models for repeated measures; MMSE, mini mental state examination; W, week.

Trial name: TRAILBLAZER-ALZ4	NCT number: NCT05108922
Objective	The study was designed to investigate amyloid plaque clearance with donanemab versus aducanumab in participants with early symptomatic AD.
Publications – title, author, journal, year	Congress: Salloway S, Lee E, Papka M, Pain A, Oru E, Ferguson MB, et al. TRAILBLAZER-ALZ 4: Topline Study Results Directly Comparing Donanemab to Aducanumab on Amyloid Lowering in Early, Symptomatic Alzheimer's Disease. BJPsych Open. 2023;9(S1):S67-S.
Study type and design	Multicenter, randomized, open-label, parallel-group, 2-arm, phase III trial (Completed).
Sample size (n)	*148 participants*
Main inclusion criteria	Age 50-85 years, gradual and progressive change in memory function reported by the participant or informant for ≥6 months, CDR-Global Score of 0.5 or 1, MMSE score of 20-30, and amyloid pathology confirmed by florbetapir F18 PET scan.
Main exclusion criteria	Significant neurological disease affecting the CNS (other than AD), current serious or unstable medical illnesses, history of clinically significant multiple or severe drug allergies, history of bleeding disorder or use of medications with platelet anti-aggregant or anti-coagulant properties (unless aspirin at ≤325 mg daily), prior or current treatment with donanemab or aducanumab, known allergies to donanemab or

Trial name: TRAILBLAZER-ALZ4	NCT number: NCT05108922
	aducanumab, and prior or current participation in any immunotherapy study targeting amyloid beta.
Intervention	Donanemab (n=71), induced with 700 mg 3x Q4W, followed by maintenance with 1400 mg Q4W up to 72 weeks.
Comparator(s)	Aducanumab (n=69) per USPI: 1 mg/kg IV Q4W (first 2 doses), 3 mg/kg IV Q4W (next 2 doses), 6 mg/kg IV Q4W (next 2 doses), and 10 mg/kg IV Q4W (subsequent doses)
Follow-up time	76 weeks
Is the study used in the health economic model?	Yes, TRAILBLAZER-ALZ4 data is used in the integrated safety analysis which in turn is used as the source for the safety data used in the model. No other data are used from this study.
Primary, secondary and exploratory endpoints	Primary: • Percentage of participants with amyloid plaque clearance (≤24.1 CL) at 6 months as assessed by florbetapir F18 PET scans Key secondary: • Mean absolute change from baseline in amyloid plaque at 6, 12, and 18 months on florbetapir PET scan. • Time to reach amyloid plaque clearance. **Endpoints included in this application:** None of the endpoints are used in the health-economic model and therefore are not considered relevant to this submission. **Other endpoints:** See above
Method of analysis	The comparison of donanemab versus aducanumab with respect to the proportion of participants achieving brain amyloid clearance at 6 months was performed using logistic regression including a fixed effect for treatment, APOE ε4 genotype, baseline amyloid level, and baseline age. Analysis was conducted on the full ITT population.
Subgroup analyses	Subgroup analyses were performed on a no/very low tau population. The following information was not reported: - characteristics of included population - method of analysis - was it pre-specified or post hoc? - assessment of validity, including statistical power for pre-specified analyses.

Trial name: TRAILBLAZER-ALZ4	NCT number: NCT05108922
Other relevant information	*N/A*

Abbreviations: AD, Alzheimer's Disease; CDR-G, Clinical Dementia Rating Scale – Global score; CNS, central nervous system; MMSE, mini mental state examination; PET, Positron emission tomography.

Trial name: TRAILBLAZER-EXT	NCT number: NCT04640077
Objective	The main goals of this study are to further determine whether the study drug donanemab is safe and effective in participants with Alzheimer's disease and to validate video scale assessments.
Publications – title, author, journal, year	N/A
Study type and design	Phase II, open-label extension study in patients with symptomatic AD who participated in the double-blind treatment period of TRAILBLAZER-ALZ or TRAILBLAZER-ALZ2 (Completed). The study was composed of two parts: part A - validation of remote scale assessments (alternating at-home and on-site cognitive and functional scale assessments) and part B - donanemab administered intravenously.
Sample size (n)	*94 participants*
Main inclusion criteria	Participated in a double-blind treatment period of a sponsor-approved originating donanemab trial, for example the TRAILBLAZER-ALZ study; have a study partner; stable symptomatic Alzheimer's Disease (AD) medications and other medication that may impact cognition for at least 30 days prior to randomization into Part A.
Main exclusion criteria	Current serious or unstable illnesses including cardiovascular, hepatic, renal, gastroenterologic, respiratory, endocrinologic, neurologic (other than AD), psychiatric, immunologic, or hematologic disease and other conditions that, in the investigator's opinion, could interfere with outcome assessments or the analyses in this study; have received treatment with a passive anti-amyloid immunotherapy after completion of originating donanemab study or received active immunization against Aβ in any other study; poor venous access; contraindication to PET or MRI imaging.
Intervention	Donanemab (n=55), open label (700 mg IV infusion Q4W x 3, then 1400 mg Q4W for up to 72 weeks).
Comparator(s)	No intervention.
Follow-up time	Up to 96 weeks

Trial name: TRAILBLAZER-EXT	NCT number: NCT04640077
Is the study used in the health economic model?	Yes, TRAILBLAZER-EXT data is used in the integrated safety analysis which in turn is used as the source for the safety data used in the model. No other data are used from this study.
Primary, secondary and exploratory endpoints	Primary: Part A: Correlation between VTC and on-site assessment for PAIR 1 for Alzheimer's Disease Assessment Scale - Cognitive Subscale (ADAS-Cog13) Part A: Correlation between VTC and on-site assessment for PAIR 1 for Alzheimer's Disease Cooperative Study Activities of Daily Living Inventory (ADCS-ADL) Part A: Correlation between VTC and on-site assessment for PAIR 1 for Mini Mental State Examination (MMSE) Score Part A: Correlation between VTC and on-site assessment for PAIR 1 for Clinical Dementia Rating-Sum of Boxes (CDR-SB) Part B: Percentage of Participants with One or More Adverse Events (AEs) or Serious AEs Secondary: Part B: Change from BL on the MMSE Score Part B: Change from BL on the ADAS-Cog13 score Part B: Change from BL on the Integrated Alzheimer's Disease Rating Scale (iADRS) Part B: Change from BL on the ADCS-iADL Part B: Change from BL on the CDR-SB Part B: Change from BL in Brain Amyloid Plaque Deposition as Measured by Florbetapir F18 Positron Emission Tomography (PET) Scan Part B: Change from BL in Brain Volume as Measured by Volumetric Magnetic Resonance Imaging (vMRI) measures Part B: Pharmacokinetics (PK): Average Serum Concentration of Donanemab Part B: Number or Participants with Anti-Donanemab Antibodies Part B: Change from BL in Columbia-Suicide Severity Rating Scale (C-SSRS) **Endpoints included in this application:** None of the endpoints are used in the health-economic model and therefore are not considered relevant to this submission. **Other endpoints:** See above

Trial name: TRAILBLAZER-EXT		NCT number: NCT04640077
Method of analysis	NR	
Subgroup analyses	Not deemed relevant	
Other relevant information	*N/A*	

Abbreviations: ADAS-Cog13, Alzheimer's Disease Assessment Scale – 13-item Cognitive subscale; ADCS-iADL, Alzheimer's Disease Cooperative Study – instrumental Activities of Daily Living subscale; BL, baseline; CDR-G, Clinical Dementia Rating Scale – Global score; CDR-SB, Clinical Dementia Rating Scale – Sum of Boxes; CL, centiloid; iADRS, integrated Alzheimer's Disease Rating Scale; Vmri, Volumetric Magnetic Resonance Imaging; W, week;.

Appendix B. Efficacy results per study

Table 56 summarizes the results for TRAILBLAZER-ALZ2 and its long-term extension.

Limitations to MMSE as an endpoint

The MMSE, while widely used for cognitive screening, is limited as a primary endpoint in clinical trials and economic modeling for AD. Its shortcomings include poor sensitivity in MCI, floor effects in advanced stages, and lack of coverage of key cognitive domains and functional abilities (147). MMSE does not measure functional domains, which are critical for assessing treatment efficacy and disease progression. As a result, EMA does not recognize MMSE as a suitable primary endpoint for AD trials. However, due to its widespread use in clinical practice, the DMC has requested data on MMSE for another amyloid-targeting therapy (53). To address this request and maintain transparency, we have chosen to present the MMSE results for TB2 exclusively in Appendix B. This approach allows us to provide the requested data while clearly emphasizing that MMSE is not an appropriate substitute for validated endpoints such as CDR-SB when evaluating clinical effectiveness and disease progression in AD (148-150)).

Results per study

Table 56 Results per study TRAILBLAZER-ALZ2

TRAILBLAZER-ALZ2 (NCT04437511)											
				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**		
iADRS least squares mean change	SmPC[b]: Donanemab	717	–10.82 (0.58)	2.65	1.04, 4.26	0.0013	19.6%	7.59%, 31.69%	0.0013	Comparison between treatment groups conducted using a conservative MMRM analysis	(5), Lilly data on file
	SmPC[b]: Placebo	730	–13.47 (0.58)								

TRAILBLAZER-ALZ2 (NCT04437511)											
				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**		
from BL at W76 (MMRM)	Eligible[a]: Donanemab	612	–10.64 (0.60)	2.32	0.69, 3.95	0.0053	17.9%	5.2%, 30.6%	0.0053		
	Eligible[a]: Placebo	601	–12.95 (0.59)								
CDR-SB least squares mean change from BL at W76 (MMRM)	SmPC[b]: Donanemab	717	1.73 (0.096)	–0.69	–0.95, –0.43	<0.0001	28.5%	17.44%, 39.51%	<0.0001	Comparison between treatment groups conducted using a conservative MMRM analysis	(5), Lilly data on file
	SmPC[b]: Placebo	730	2.42 (0.097)								
	Eligible[a]: Donanemab	612	1.70 (0.108)	-0.67	-0.97, -0.37	<0.0001	28.2%	15.2%, 41.3%	<0.0001		
	Eligible[a]: Placebo	601	2.37 (0.116)								
	SmPC[b]: ADNI cohort	95	NR								
CDR-SB change from	SmPC[b]: Donanemab Early-start	352	NR	-1.0	-1.5, -0.4						(6), Lilly data on file

TRAILBLAZER-ALZ2 (NCT04437511)											
				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**		
baseline with ADNI matched controls in the LTE (36 months)	SmPC[b]: ADNI cohort	95	NR								
	SmPC[b]: Donanemab Delayed-start	381	NR	-0.6	-1.2, -0.0						
	SmPC[b]: ADNI cohort	109	NR								
ADCS-iADL least squares mean change from BL at W76 (MMRM)	SmPC[b]: Donanemab	717	–4.91	1.46	0.50, 2.42	0.0028	23.0%	7.70%, 38.24%	0.0028	Comparison between treatment groups conducted using a conservative MMRM analysis	(5), Lilly data on file
	SmPC[b]: Placebo	730	–6.37								
	Eligible[a]: Donanemab	612	–4.70	1.24	0.23, 2.26	0.0162	20.9%	3.7%, 38.2%	0.0162		
	Eligible[a]: Placebo	601	–5.95								

TRAILBLAZER-ALZ2 (NCT04437511)											
				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-Cog_{13} least squares mean change from BL at W76 (MMRM)	SmPC[b]: Donanemab	717	5.67	–1.35	–2.19, –0.51	0.0016	19.3%	7.21%, 31.30%	0.0016	Comparison between treatment groups conducted using a conservative MMRM analysis	(5), Lilly data on file
	SmPC[b]: Placebo	730	7.03								
	Eligible[a]: Donanemab	612	5.57	-1.37	-2.28, -0.45	0.0034	19.7%	6.4%, 33.1%	0.0034		
	Eligible[a]: Placebo	601	6.94								
Proportion of participants with amyloid clearance at W76 (Fisher's exact test)	SmPC[b]: Donanemab	692	80.8% (77.15, 83.95)	NR	NR	<0.0001	NR	NR	NR	Comparison between treatment groups conducted using a Fisher's exact test	(5), Lilly data on file
	SmPC[b]: Placebo	713	0.2%								
	Eligible[a]: Donanemab	593	80.5% (76.6, 83.9)	NR	NR	<0.0001	NR	NR	NR		
	Eligible[a]: Placebo	587	0.0% (0.0, 0.8)								

TRAILBLAZER-ALZ2 (NCT04437511)											
				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 participants with amyloid clearance at W24 (Fisher's exact test)	SmPC[b]: Donanemab	692	32.5%	NR	NR	<0.0001	NR	NR	NR	Comparison between treatment groups conducted using a Fisher's exact test	(5), Lilly data on file
	SmPC[b]: Placebo	713	0.2%								
	Eligible[a]: Donanemab	593	33.5% (29.63, 37.51)	NR	NR	<0.0001	NR	NR	NR		
	Eligible[a]: Placebo	587	0.2%								
MMSE least squares mean change from BL at W76	SmPC[b]: Donanemab	717	NR	0.40	–0.015, 0.808	0.0587	13.2%	–0.54, 26.86	0.0587	Comparison between treatment groups conducted based on a conservative analysis	(5), Lilly data on file
	SmPC[b]: Placebo	730	NR								
	Eligible[a]: Donanemab	612	NR	0.61	0.16, 1.06	0.0085	19.5%	4.9%, 34.2%	0.0085		
	Eligible[a]: Placebo	601	NR								

TRAILBLAZER-ALZ2 (NCT04437511)											
				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**		
CDR-G risk of progression to a later clinical stage at week 76 (Cox PHM TTE)	SmPC[b]: Donanemab	672	22.8% (19.8%; 26.1%)	NR	NR	NR	40.3% HR 0.597	HR 0.47, 0.75	<0.0001	Comparison between treatment groups conducted using Cox proportional hazard modelling	(5), Lilly data on file
	SmPC[b]: Placebo	701	34.4% (31.0%; 38.0%)								
	Eligible[a]: Donanemab	565	30.8% 27.1%; 34.7%)	NR	NR	NR	47.2% HR 0.528	HR 0.30, 0.92	0.0238		
	Eligible[a]: Placebo	567	43.6% (39.5%; 47.7%)								
CDR-G risk of progression to moderate clinical stage at week 76 (Cox PHM TTE)	SmPC[b]: Donanemab	664	NR	NR	NR	NR	HR 0.520	0.33, 0.83	0.0060	Comparison between treatment groups conducted using Cox proportional hazard modelling	(5), Lilly data on file
	SmPC[b]: Placebo	687	NR								
	Eligible[a]: Donanemab	565	NR	NR	NR	NR	47.2% HR 0.528	HR 0.30, 0.92	0.0238		
	Eligible[a]: Placebo	567	NR								

TRAILBLAZER-ALZ2 (NCT04437511)											
				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		
iADRS risk of meaningful within-participant disease progression, BL to W76 (MWPC) (Cox PHM TTE)	SmPC[b]: Donanemab	657	30.1% (26.8%; 33.8%)	NR	NR	NR	31.9% HR 0.681	HR 0.55, 0.84	<0.001	Comparison between treatment groups conducted using Cox proportional hazard modelling	(5), Lilly data on file
	SmPC[b]: Placebo	690	40.0% (36.4%; 43.7%)								
	Eligible[a]: Donanemab	567	30.2% (26.5%; 34.1%)	NR	NR	NR	29.1% HR 0.709	HR 0.56, 0.89	0.004		
	Eligible[a]: Placebo	570	39.1% (35.2%; 43.2%)								
CDR-SB Risk of meaningful within-participant disease progression, BL to W76 (MWPC)	SmPC[b]: Donanemab	670	28.7% (25.4%; 32.2%)	NR	NR	NR	36.4% HR 0.636	HR 0.52, 0.78	<0.001	Comparison between treatment groups conducted using Cox proportional hazard modelling	(5), Lilly data on file
	SmPC[b]: Placebo	699	40.6% (37.0%; 44.3%)								
	Eligible[a]: Donanemab	580	28.4% (24.9%; 32.3%)	NR	NR	NR	38% HR 0.620	HR 0.49, 0.78	<0.001		
	Eligible[a]: Placebo	579	40.4% (36.5%; 44.5%)								

TRAILBLAZER-ALZ2 (NCT04437511)											
				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**		
(Cox PHM TTE)											
iADRS disease progression delayed at W76, months saved (Time-PMRM)	SmPC[b]: Donanemab	648	NR	Months saved: 2.86 % time saved: 16.33%	Months saved: 1.27, 4.46 % time saved: 7.25, 25.41	<0.001	NR	NR	NR	Comparison between treatment groups conducted using a time-progression model for repeated measures	(5), Lilly data on file
	SmPC[b]: Placebo	684	NR								
	Eligible[a]: Donanemab	NR	NR	NR	NR	NR	NR	NR	NR		
	Eligible[a]: Placebo	NR	NR								
CDR-SB disease progression delayed at W76, months saved	SmPC[b]: Donanemab	663	NR	Months saved: 5.82 % time saved: 33.17%	Months saved: 4.2, 7.44 % time saved: 23.95, 42.4	<0.001	NR	NR	NR	Comparison between treatment groups conducted using a time-progression model for repeated measures	(5), Lilly data on file
	SmPC[b]: Placebo	694	NR								

TRAILBLAZER-ALZ2 (NCT04437511)											
				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**		
(Time-PMRM)	Eligible[a]: Donanemab	NR	NR	NR	NR	NR	NR	NR	NR		
	Eligible[a]: Placebo	NR	NR								
CDR-SB no progression at 52 weeks (probability of disease progression free) (GLMM)	SmPC[b]: Donanemab	584	39% (0.35, 0.43)	NR	NR	0.00001	NR	NR	NR	Comparison between treatment groups conducted using a generalised linear mixed model	(5), Lilly data on file
	SmPC[b]: Placebo	582	25% (0.21, 0.28)								
	Eligible[a]: Donanemab	481	37% (0.32, 0.41)	NR	NR	<.00001	NR	NR	NR		
	Eligible[a]: Placebo	478	22% (0.19, 0.26)								
Change from BL in amyloid plaque levels at	SmPC[b]: Donanemab	637	–90.39 [0.99]	–89.24	–91.95, –86.54	<0.0001	NR	NR	NR	Comparison between treatment groups conducted using a model for repeated measures	(5), Lilly data on file
	SmPC[b]: Placebo	670	–1.15 [0.96]								

TRAILBLAZER-ALZ2 (NCT04437511)											
				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**		
W76, CL (MMRM)	Eligible[a]: Donanemab	551	–89.58 [1.08]	-87.80	-90.68, -84.91	<0.0001	NR	NR	NR		
	Eligible[a]: Placebo	552	–1.78 [1.07]								

[a] EU eligible population includes all randomised participants in TRAILBLAZER-ALZ2 excluding APOE ε4 homozygotes, patients with baseline superficial siderosis, poorly controlled blood pressure defined as systolic blood pressure ≥140mmHg and diastolic blood pressure ≥90mmHG and anticoagulant use. 5 patients are included with missing APOE4 information.

[b] EU SmPC population includes all randomised participants in TRAILBLAZER ALZ2 excluding *APOE* ε4 homozygotes.

Abbreviations: ADAS-Cog13, Alzheimer's Disease Assessment Scale – 13-item Cognitive subscale; ADCS-iADL, Alzheimer's Disease Cooperative Study – instrumental Activities of Daily Living subscale; BL, baseline; CDR-G, Clinical Dementia Rating Scale – Global score; CDR-SB, Clinical Dementia Rating Scale – Sum of Boxes; CL, centiloid; GFAP, glial fibrillary acidic protein; GLMM, generalised linear mixed model; iADRS, integrated Alzheimer's Disease Rating Scale; MMRM, mixed models for repeated measures; MMSE, mini mental state examination; MWPC, meaningful within person change; NCS2, natural cubic spline model with 2 degrees of freedom; NfL, neurofilament light chain; NR, not reported; PMRM, progression model for repeated measures; SUVR, standard uptake value ratio; TTE, time-to-event; W, week.

Appendix C. Comparative analysis of efficacy

Not applicable.

Table 57 Comparative analysis of studies comparing [intervention] to [comparator] for patients with [indication]

Outcome		Absolute difference in effect			Relative difference in effect			Method used for quantitative synthesis	Result used in the health economic analysis?
	Studies included in the analysis	Difference	CI	P value	Difference	CI	P value		
Not applicable.									

Appendix D. Extrapolation

D.1 Extrapolation of CDR-SB

D.1.1 Data input

Data from TRAILBLAZER-ALZ2, supported by the long-term extension study, was used, as described in Section 8.1.2.

D.1.2 Model

The chosen model was the Cox proportional hazards model.

D.1.3 Proportional hazards

The proportional hazard assumption for the Cox proportional model used to estimate the HR of progressing to clinical worse health states in CDR-SB in the overall population were visually assessed with:

- The Kaplan–Meier curves
- The log cumulative hazard plot
- The standardized Schoenfeld residuals of (151)
    - The standardized Schoenfeld residuals were generated with the R package after fitting the Cox proportional hazard model with the same covariates used to estimate the donanemab treatment effect (i.e., adjusting for baseline age, score, and concomitant AChEI and/or memantine use at baseline (yes/no), and stratifying by pooled investigator sites, and baseline tau category)

Cox proportional hazard assumption using CDR-SB:

Figure 18 displays the Kaplan–Meier curves for each treatment arms of the TRAILBLAZER-ALZ2 data and Figure 19 displays the log cumulative hazards. The steps seen in both the Kaplan–Meier and log cumulative hazard curves correspond to the scheduled visits as per protocol. Figure 20 displays the smoothed standardized Schoenfeld residuals over time, with associated 95% CI, and the p-value of the test performed on these residuals (with the null hypothesis that the slope of these residuals over time equals to zero). A “no effect” horizontal line was added in red color.

Based on visual assessment of the Kaplan–Meier curves (curves are not crossing) and on the log cumulative hazard plot (parallel hazards), there is evidence that the proportional hazards assumption holds. In addition, the inspection of the smoothed standardized Schoenfeld residuals over time, adds evidence that the hazards are proportional as they constitute an approximate horizontal line. Finally, the p-value from the test performed on those residuals is *P*=0.506 suggesting that the assumption of slope=0 for those

residuals cannot be rejected. In other words, there is no evidence of violation of the proportional hazard assumption; the treatment effect is constant over time.

Figure 18 Kaplan–Meier Curves for TRAILBLAZER-ALZ2 Trial Using CDR-SB

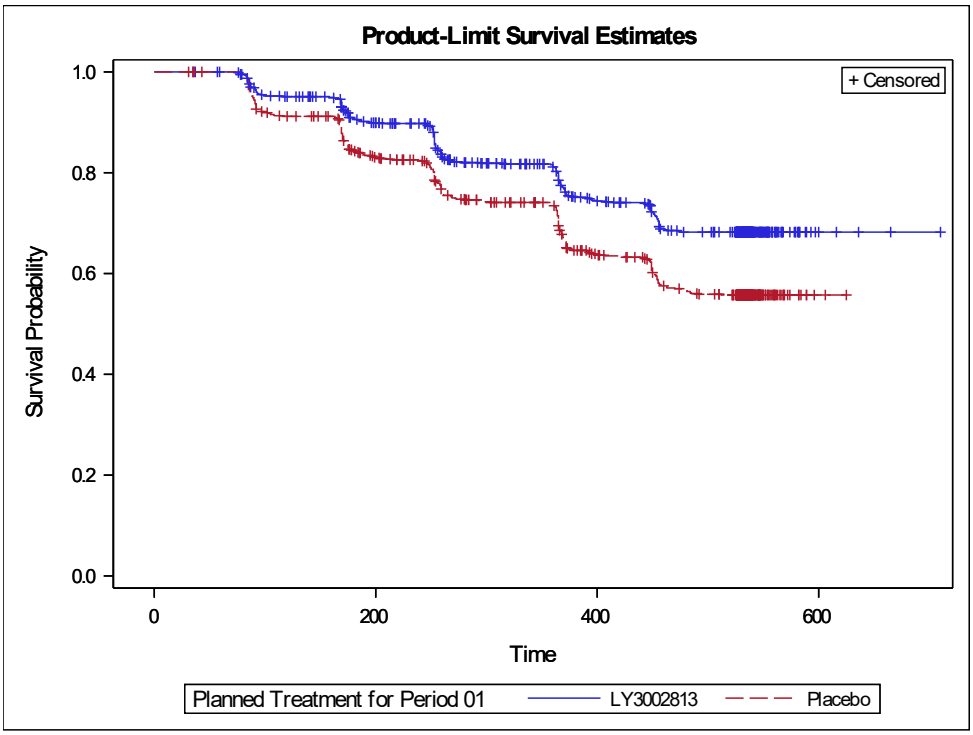


Figure 19 Log Cumulative Hazard Plot for TRAILBLAZER-ALZ2 Trial Using CDR-SB

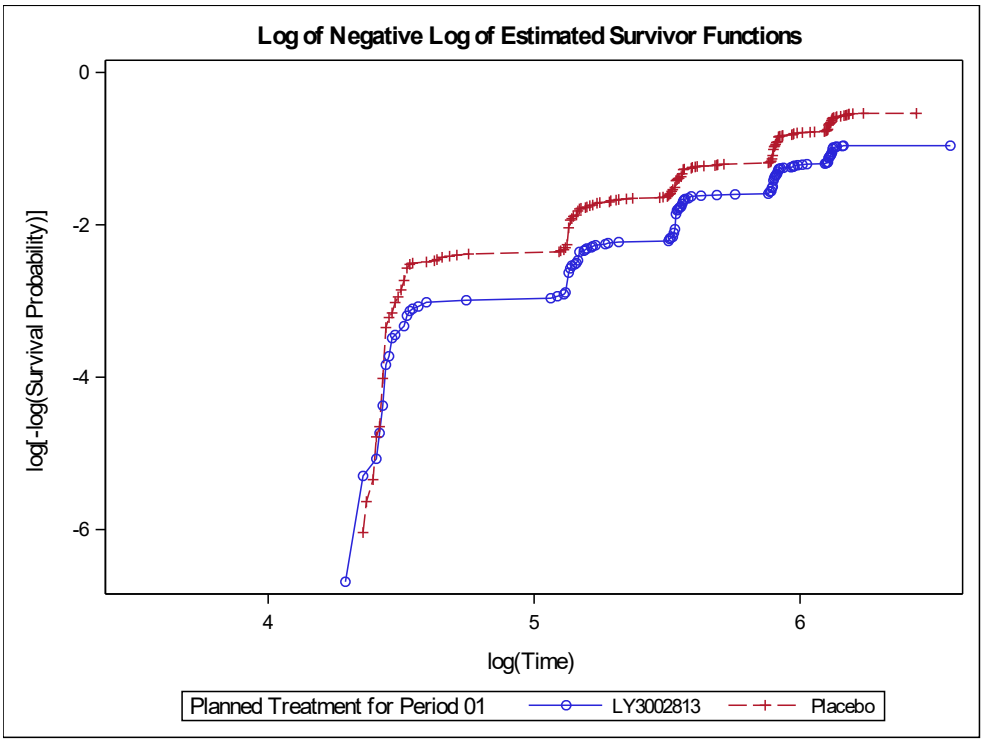
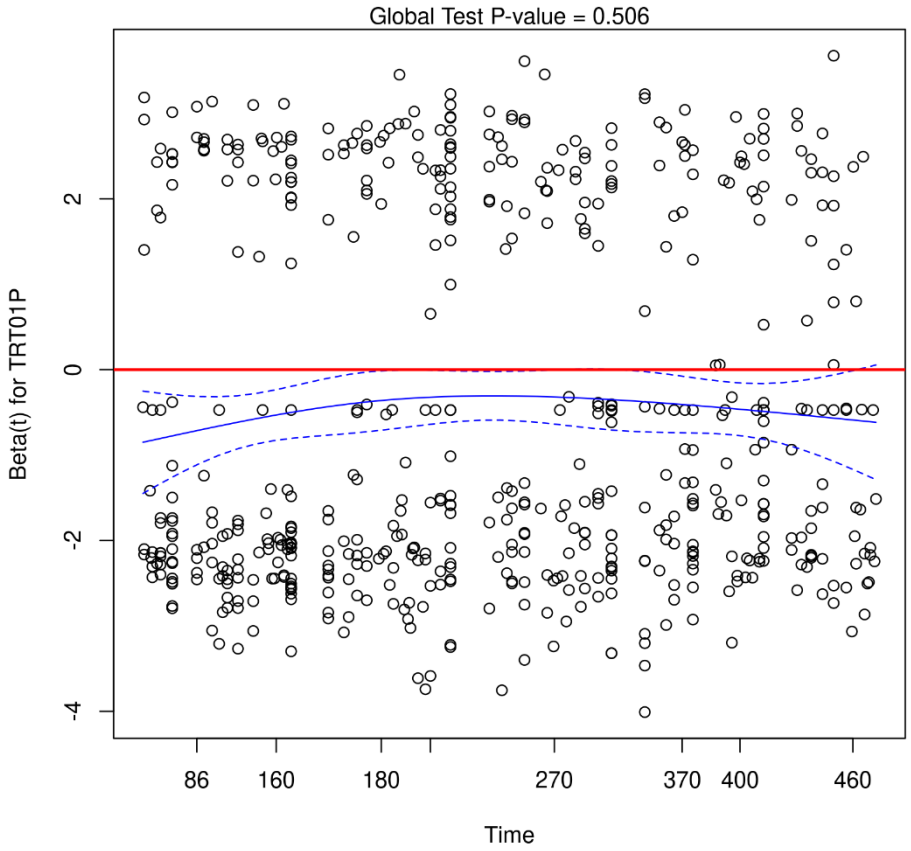


Figure 20 Schoenfeld Residuals Plot for TRAILBLAZER-ALZ2 Trial Using CDR-SB



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

N/A

D.1.5 Evaluation of visual fit

Figure 18 and Figure 19 are considered to support the assumption of a constant hazard ratio equal to 0.62 between the treatment arms throughout the 18-month study data. This is further supported by data from the TRAILBLAIZER-ALZ2 long-term extension study, showing a persistent treatment effect over a 3-year period (Figure 33).

D.1.6 Evaluation of hazard functions

N/A

D.1.7 Validation and discussion of extrapolated curves

The long-term trajectory for the comparator arm is based on epidemiological data and therefore should be valid as long as those data are representative of the treated population. There is no long-term data beyond 3 years for participants in the treatment arm, but it is reasonable to assume that they have a slower progression than the comparator arm and simulated in the model.

D.1.8 Adjustment of background mortality

Mortality is modelled as described in Section 8.1.2.

D.1.9 Adjustment for treatment switching/cross-over

N/A, as all patients are assumed to complete treatment with donanemab at 18 months (at the latest).

D.1.10 Waning effect

Described in Section 8.4.

D.1.11 Cure-point

N/A

D.2 Extrapolation of [effect measure 2]

N/A

Appendix E. Serious adverse events

The relevant serious adverse events are reported in Section 9.

Appendix F. Health-related quality of life

Caregiver characteristics

As mentioned in Appendix J, Johansson et al from 2021 was used as source for caregiver characteristics (i.e., number of caregivers per patient, proportion of child caregivers, mean age of child caregivers, proportion of child caregivers that were females, proportion of spouse caregivers, mean age of spouse caregivers, proportion of spouse caregivers that were females), thus it was chosen to inform these assumptions in the model. The data was considered relevant for the Danish setting.

Caregiver utilities

Study design

Caregiver utility inputs were modeled by AD severity stage based on two health state vignette studies (Belger et al, 2022 (152); Eli Lilly 2024a). Both studies used a cross-sectional design to assess health state utilities associated with caregiving for individuals with Alzheimer's disease. Belger (2022) (152) used face-to-face TTO interviews with UK general-population participants, explicitly instructing them to imagine themselves as the caregiver when valuing vignette health states for mild, moderate, and severe AD dementia. Matza (2024) (135) used interviewer-administered TTO with general-population participants in the UK and US to value caregiver vignettes spanning MCI, mild, and moderate AD. The studies aimed to quantify the impact of caregiving on health-related quality of life.

Caregiver utilities are not part of the base case in line with DMC guidelines, however due to the high burden of disease and the significant strain on relatives providing home care in Denmark (46), scenarios including this information have been included.

Data collection

Matza et al. (2024) (135) and Belger et al. (2022) (136) both collected data using vignette-based TTO interviews with general population samples. Matza et al. valued six caregiving vignettes across UK and US participants (N=506), while Belger et al. used six similar vignettes in face-to-face TTO interviews with 109 UK respondents.

HSUV results

Caregivers' utility values based on Belger et al. (2022) (136) and Matza et al (2024) (135) are presented in Table 58.

Table 58 Overview of literature-based health state utility values (caregivers)

	Results	Instrument	Tariff (value set) used	Comments
Caregiver's HSUV - Child Caregiver				
MCI due to AD - community and institutionalised	0.840	TTO	-	Community: Matza 2024 (135) Institutionalised: assume the same utilities as community.
Mild AD Dementia - community and institutionalised	0.775	TTO	-	Community: Matza 2024 (135) Institutionalised: assume the same utilities as community.
Moderate AD Dementia - community	0.615	TTO	-	Community: Matza 2024 (135)
Moderate AD Dementia - institutionalised	0.710	TTO	-	Institutionalised: Belger 2022 (136); caregiver living separately from parent with AD.
Severe AD Dementia - community	0.455	TTO	-	Community: Matza 2024 (135); Belger 2022 (136)
Severe AD Dementia - institutionalised	0.640	TTO	-	Institutionalised: Belger 2022; caregiver living separately from parent with AD in nursing home.
Caregiver's HSUV- Spouse Caregiver				
MCI due to AD - community and institutionalised	0.813	TTO	-	Assume the same utilities as the general population.
Mild AD Dementia - community and institutionalised	0.715	TTO	-	Community: Matza 2024 (135) Institutionalized: assume the same utilities as community.
Moderate AD Dementia - community	0.542	TTO	-	Community: Matza 2024 (135)
Moderate AD Dementia - institutionalised	0.710	TTO	-	Institutionalised: Belger 2022 (136)

	Results	Instrument	Tariff (value set) used	Comments
Severe AD Dementia - community	0.382	TTO	-	Community: Matza 2024 (135)
Severe AD Dementia - institutionalised	0.640	TTO	-	Institutionalised: Belger 2022 (136)

Abbreviations: AD dementia, Alzheimer's disease; ARIA, amyloid-related imaging abnormalities; MCI, mild cognitive impairment.

Appendix G. Probabilistic sensitivity analyses

Table 59 presents an overview of all the parameters included in the PSA. All parameters relevant for the present analysis were included in the PSA. The assumptions and data for the PSA can be found in the model on the 'PSA Inputs' sheet.

Table 59. Overview of parameters in the PSA

Input parameter	Point estimate	Alpha	Beta	Probability distribution
Patient Characteristics				
Baseline Population - Proportion MCI due to AD Severity at Initiation	50.00%	49.5	49.5	Beta
Percent Male - MCI due to AD Severity at Initiation	50.40%	95.88330315	94.36134596	Beta
Percent Male - Mild AD Dementia Severity at Initiation	43.00%	313.9222525	416.1294975	Beta
Population Age MCI due to AD Severity at Initiation [years]	70.0 years	-	-	Normal
Population Age Mild AD Dementia Severity at Initiation [years]	70.0 years	-	-	Normal
Disease Progression				
Natural Progression of Disease	Multivariate	-	-	Dirichlet (Multivariate Beta)
Risk of Institutionalization by Disease Stage				
MCI due to AD	0.000	0	0	Beta
Mild AD Dementia	0.000	0	0	Beta
Moderate AD Dementia	0.080	18.923857	217.6243556	Beta

Severe AD Dementia	0.10	9.041225461	81.37102915	Beta
HR vs BSC on CDR-SB Scale				
HR vs BSC on CDR-SB Scale for Donanemab - MCI due to AD	0.62	-	-	Lognormal
HR vs BSC on CDR-SB Scale for Donanemab - Mild AD Dementia	0.62	-	-	Lognormal
HR vs BSC on CDR-SB Scale for Donanemab - Moderate AD Dementia	0.62	-	-	Lognormal
Treatment discontinuation				
Treatment Discontinuation due to Amyloid Clearance				
Proportion Stopping Treatment for Donanemab at 6 months	0%	0	0	Beta
Proportion Stopping Treatment for Donanemab at 12 months	69.70%	344.0577678	149.5688718	Beta
Proportion Stopping Treatment for Donanemab at 18 months	10.80%	2497.961549	20631.31205	Beta
Proportion Stopping Treatment for Donanemab at 24 months	0%	0	0	Beta
Proportion Stopping Treatment for Donanemab at 30 months	0%	0	0	Beta
Proportion Stopping Treatment for Donanemab at 36 months	0%	0	0	Beta

Treatment completion for Positive Stopping Rules - Start of Treatment Effect Waning				
Donanemab	Cycle 13	100	0.13	Gamma
Treatment Discontinuation for Negative Stopping Rules - % that Discontinue after 6 months				
Donanemab	8.86%	76.11392405	782.8860759	Beta
Treatment Discontinuation for Adverse Events - Start of Treatment Effect Waning				
Donanemab	Cycle 2	100	0.02	Gamma
Treatment Discontinuation for Adverse Events - Duration Tx Effect Post-Discontinuation				
Donanemab	5 cycles	100	0.05	Gamma
Treatment Discontinuation for Adverse Events - % of Full Treatment Effect Retained				
Donanemab	0%	0%	0%	Beta
% Patients Screened for Amyloid Clearance				
% Patients Screened for Amyloid Clearance - Donanemab	1	-1	0	Beta
Treatment and Treatment Related Costs				
RDI				
RDI for Donanemab - Treatment Start	97.28%	100	0.009727527	Gamma
RDI for Donanemab - 3	97.28%	100	0.009727527	Gamma
RDI for Donanemab - 12	97.28%	100	0.009727527	Gamma
Administration Costs by Method				
Unit Cost for Infusion: 1st hour	DKK2,061.00	100	20.61	Gamma
Unit Cost for Infusion: Subsequent Hour	DKK -	0	0	Gamma
Mode and Duration of Admin - Admin Duration				

Admin Duration for Donanemab	1.0 hour	-	-	Normal
Concomitant Medications				
Annual Cost of Acetylcholinesterase inhibitor	DKK 115.35	100	1.15347449	Gamma
Annual Cost of Memantine	DKK 68.57	100	0.6857	Gamma
Use of Acetylcholinesterase inhibitor for MCI due to AD	0.000	0	0	Beta
Use of Acetylcholinesterase inhibitor for Mild AD Dementia	0.800	19.2	4.8	Beta
Use of Acetylcholinesterase inhibitor for Moderate AD Dementia	0.700	29.3	12.55714286	Beta
Use of Acetylcholinesterase inhibitor for Severe AD Dementia	0.650	34.35	18.49615385	Beta
Use of Memantine for MCI due to AD	0.000	0	0	Beta
Use of Memantine for Mild AD Dementia	0.015	98.485	6467.181667	Beta
Use of Memantine for Moderate AD Dementia	0.200	79.8	319.2	Beta
Use of Memantine for Severe AD Dementia	0.250	74.75	224.25	Beta
Resource Utilization Costs				
Imaging/Testing Unit Costs				

Unit Cost for MRI Scan	DKK 2,638.00	100	26.38	Gamma
Unit Cost for Amyloid PET Scan	DKK 4,681.00	100	46.81	Gamma
Unit Cost for Blood-Based Biomarkers	DKK 1,000.00	100	10	Gamma
Unit Cost for Amyloid CSF	DKK 4,337.00	100	43.37	Gamma
Unit Cost for APOE ε4 Test	DKK 3,112.00	100	31.12	Gamma
Adverse Events Monitoring				
# Units used for ARIA Events Monitoring for Donanemab	5	-	-	Normal
Direct Medical Annual Costs - Community				
Direct medical costs (medication, hospitalization) - MCI due to AD	DKK 70,685.20	100	706.8520356	Gamma
Direct medical costs (medication, hospitalization) - Mild AD Dementia	DKK 126,223.58	100	1262.235778	Gamma
Direct medical costs (medication, hospitalization) - Moderate AD Dementia	DKK 117,632.90	100	1176.328968	Gamma
Direct medical costs (medication, hospitalization) - Severe AD Dementia	DKK 110,866.21	100	1108.662081	Gamma
Direct Medical Annual Costs - Institutionalized				
Direct medical costs (medication, hospitalization) (Institutionalization) - MCI due to AD	DKK 357,114.27	100	3571.14266	Gamma

Direct medical costs (medication, hospitalization) (Institutionalization) - Mild AD Dementia	DKK 637,704.05	100	6377.040465	Gamma
Direct medical costs (medication, hospitalization) (Institutionalization) - Moderate AD Dementia	DKK 523,823.41	100	5238.234109	Gamma
Direct medical costs (medication, hospitalization) (Institutionalization) - Severe AD Dementia	DKK 524,825.16	100	5248.251631	Gamma
Distribution of Diagnostic Testing Resources				
Donanemab - MRI Scan	113.00%	100	0.0113	Gamma
Donanemab - Amyloid PET Scan	-%	0	0	Gamma
Donanemab - Blood-Based Biomarkers	-%	0	0	Gamma
Donanemab - Amyloid CSF	-%	0	0	Gamma
Donanemab - APOE ε4 Test	118.00%	100	0.0118	Gamma
Adverse Events				
Incidence Rate of All-Grade ARIA Events and Serious AEs (Grade 3+) over Trial Period				
Donanemab - ARIA Event	23.42%	199.5189873	652.4810127	Beta
Distribution of ARIA-E Events				
% Symptomatic ARIA-E for Donanemab	11.54%	23.53846154	180.4615385	Beta
Adverse Event Costs				

Cost for ARIA Event	DKK 7,337.00	100	73.37	Gamma
Cost for Infusion Related Reactions	DKK 5.74	100	0.057442	Gamma
Cost for Hypersensitivity	DKK 5.74	100	0.057442	Gamma
Cost for Anaphylactic Reaction	DKK 5,762.00	100	57.62	Gamma
Utility				
Patient Baseline Health State Utility - Community				
MCI due to AD	0.813	17.887	4.114230012	Beta
Mild AD Dementia	0.74	218.0406566	76.60887936	Beta
Moderate AD Dementia	0.59	37.48479122	26.04875322	Beta
Severe AD Dementia	0.36	11.34386301	20.16686757	Beta
Patient Baseline Health State Utility - Institutionalized				
MCI due to AD	0.813	17.887	4.114230012	Beta
Mild AD Dementia	0.74	218.0406566	76.60887936	Beta
Moderate AD Dementia	0.59	37.48479122	26.04875322	Beta
Severe AD Dementia	0.36	11.34386301	20.16686757	Beta
Patient Age				
Patient age	78 years	-	-	Normal
AE Disutilities				
ARIA Event	- 0.14	-1.971088022	0.099751345	Lognormal
Infusion Related Reactions	-	-	-	Lognormal
Hypersensitivity	-	-	-	Lognormal
Anaphylactic Reaction	- 0.116	-2.155053787	0.099751345	Lognormal

AE Duration				
ARIA Event	61.9 days	-	-	Normal
Infusion Related Reactions	1.0 day	-	-	Normal
Hypersensitivity	1.0 day	-	-	Normal
Anaphylactic Reaction	30.0 days	-	-	Normal
Mortality				
Treatment-Related Mortality in Cycle 1				
Treatment-Related Mortality in Cycle 1 for Donanemab	0.63%	99.36075949	15599.63924	Beta
Mortality HR: Community Setting vs General Population				
Mortality HR: Community Setting vs General Population for MCI due to AD	1.00	-	-	Lognormal
Mortality HR: Community Setting vs General Population for Mild AD Dementia	1.79	-	-	Lognormal
Mortality HR: Community Setting vs General Population for Moderate AD Dementia	1.75	-	-	Lognormal
Mortality HR: Community Setting vs General Population for Severe AD Dementia	3.41	-	-	Lognormal
Mortality HR: Institutionalized vs Community Setting				
Mortality HR: Institutionalized vs Community Setting	1	-	-	Lognormal

Appendix H. Literature searches for the clinical assessment

Not applicable.

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

Table 60 Bibliographic databases included in the literature search

Database	Platform/source	Relevant period for the search	Date of search completion
Embase	e.g. Embase.com	E.g. 1970 until today	dd.mm.yyyy
Medline			dd.mm.yyyy
CENTRAL	Wiley platform		dd.mm.yyyy

Abbreviations:

Table 61 Other sources included in the literature search

Source name	Location/source	Search strategy	Date of search
e.g. NICE	www.nice.org.uk		dd.mm.yyyy
e.g. EMA website			dd.mm.yyyy

Abbreviations:

Table 62 Conference material included in the literature search

Conference	Source of abstracts	Search strategy	Words/terms searched	Date of search
Conference name	e.g. conference website	Manual search	List individual terms used to search in the conference material:	dd.mm.yyyy
	Journal supplement [insert reference]	Skimming through abstract collection		dd.mm.yyyy

H.1.1 Search strategies

Table 63 of search strategy table for [name of database]

No.	Query	Results
#1		88244
#2		85778
#3		115048
#4		7011
#5		10053
#6		12332
#7		206348
#8		211070
#9	#7 OR #8	272517
#10	#3 AND #6 AND #9	37

H.1.2 Systematic selection of studies

Table 64 Inclusion and exclusion criteria used for assessment of studies

Clinical effectiveness	Inclusion criteria	Exclusion criteria	Changes, local adaption
Population			
Intervention			
Comparators			
Outcomes			
Study design/publication type			
Language restrictions			

Table 65 Overview of study design for studies included in the analyses

Study/ID	Aim	Study design	Patient population	Intervention and comparator (sample size (n))	Primary outcome and follow-up period	Secondary outcome and follow-up period
Study 1						
Study 2						

H.1.3 Excluded full text references

H.1.4 Quality assessment

H.1.5 Unpublished data

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

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

Cost-effectiveness analyses: Research question 1

Objective of literature search: What is the modelling approach and what are the characteristics and results of economic models used to assess the cost-effectiveness of treatments for Alzheimer's disease across the continuum of disease (i.e., from mild cognitive impairment due to Alzheimer's disease [MCI-AD] through to severe dementia due to Alzheimer's disease)?

Sources: Systematic literature searches were conducted via OvidSP® (http://ovidsp.ovid.com/) in the electronic literature databases mentioned in Table 66. Additionally, websites of the HTA bodies that post appraisal reports online were searched for relevant data or references not captured by the search in order to inform the structure and inputs of the cost-effectiveness model. Moreover, CTAD and AAIC were manually hand searched to identify relevant materials published over the past five years (2020-2025). The most recent ISPOR proceeding were indexed in Embase at the time bibliographic searches were conducted therefore, no manual searches were conducted for this source.

Table 66 Bibliographic databases included in the literature search

Database	Platform	Relevant period for the search	Date of search completion
Embase	OvidSP	2012-2025	25.06.2025
MEDLINE and MEDLINE In-Process			
The Cochrane Library (CENTRAL and CDSR)			
EconLit			
NHS Economic Evaluations Database (NHS EED)*			

Database	Platform	Relevant period for the search	Date of search completion
International HTA Database (INAHTA)			
Database of Abstract Reviews of Reviews of Effects (DARE)	CRD		

Abbreviations:

*The Database of Abstracts of Reviews of Effects [DARE] and the National Health Service Economic Evaluations Database [NHS EED] databases included in the original SLR (project ID: 2021-10885) were discontinued in 2015. As a result, no new records were identified from these databases in subsequent updates.

Table 67 Other sources included in the literature search

Source name	Location/source	Search strategy	Date of search
NICE	www.nice.org.uk	Websites of the HTA bodies that post appraisal reports online were searched for relevant data or references not captured by the search in order to inform the structure and inputs of the cost-effectiveness model.	2025
SMC	SMC | Scottish Medicines Consortium		
HAS	Haute Autorité de Santé - Professional (has-sante.fr)		
PBAC	Pharmaceutical Benefits Scheme (PBS) | Public Summary Documents		
CADTH	CADTH | CADTH		
ICER	ICER | Working Towards Fair Pricing, Fair Access, & Future Innovation		

Table 68 Conference material included in the literature search

Conference	Source of abstracts	Search strategy	Words/terms searched	Date of search
ISPOR	https://www.ispor.org/	Electronic search	NR	2025
CTAD	ctad-alzheimer.com	Manual search		

Conference	Source of abstracts	Search strategy	Words/terms searched	Date of search
AAIC	https://aaic.alz.org/			

I.1.1 Search strategies

The study selection process involved evaluating publications retrieved by the searches against predetermined population, interventions and comparisons, outcomes, and study design (PICOS) criteria (Table 69) to establish which studies are eligible for inclusion in the SLRs. The utilities/HRQoL review was conducted based on a single study protocol originally approved in October 2022 and last updated in June 2025. Ultimately, the study was included only if it met all of the inclusion criteria and none of the exclusion criteria.

Table 69 Inclusion and exclusion criteria

	Inclusion	Exclusion
Population	• Patients (≥18 years) with symptomatic mild cognitive impairment (MCI) due to Alzheimer's Disease (AD) or dementia due to AD (i.e., from mild cognitive impairment due to AD through to severe dementia due to AD) • Care partners of patients with AD across the continuum of disease	• Studies not evaluating patients with symptomatic MCI due to AD or dementia due to AD or patients who were less than 18 years old • Studies investigating a mixed population of patients with dementia or MCI that did not clearly state the proportion of patients with early symptomatic AD • Studies where < 80% of the study population had AD and where data were not reported separately for the population of interest • Studies investigating AD populations with specific comorbidities (e.g., depression)
Interventions	Any intervention (or none required)	N/A
Comparators	Any intervention (or none required)	N/A

Outcomes	• Utilities/disutilities for both patients and care partner
	• CFB in the following disease specific and generic HRQoL measures (proxy- or patient reported):*
	  • SF-36
	  • EQ-5D
	  • Health Utilities Index
		Relevant outcomes are not reported

	• QoL-AD • DEMQoL • DQOL	
Study Design	Observational studies, including prospective and retrospective cohort studies, vignette studies, and cross-sectional surveys	• Editorial, erratum, trial protocol, guideline, case report, narrative review, etc. • In vitro, ex vivo, animal, or pharmacokinetic studies, phase 1 trials, etc. • Clinical trials
Other limits	• Language: English language** • Publication date: full-text original articles published since 2012 or abstracts from select conferences published since 2020 • Geography: No limit	

*Data from studies reporting only HRQoL measures with no utility outcomes will not be extracted

** No language limits were be applied in the search however, only English language articles were eligible for inclusion in the SLR.

Table 70 Search strategy for Embase

No.	Query
1	alzheimer*.ti,ab.
2	((mild* or early* or preclinical or pre-clinical) adj2 (cognitive impair* or cognitive dysfunction or cognitive decline)).ti,ab.
3	or/1-2
4	Cost-Benefit Analysis/ or Cost-Benefit Analysis.mp.
5	cost minimization analysis/ or cost minimiation.mp.
6	economic evaluation/ or economic evaluation.mp.
7	cost-effectiveness analysis/ or (cost effective* or CEA).mp.
8	cost utility analysis/ or (cost utilit* or CUA).mp.
9	Economics, Hospital/ or Economics/ or Economics, Nursing/ or Economics, Medical/ or Economics, Pharmaceutical/
10	(economic* or pharmacoeconomic* or (pharmaco adj1 economic*)).ti.
11	Monte carlo.mp.
12	decision tree.mp. or "decision tree"/
13	(decision adj3 (tree* or analys* or model*)).mp.
14	Models, Statistical/ or Markov Chains/ or (markov and (economic* or model*)).mp.

15	(patient adj2 simulat*).mp.
16	(discrete adj2 (choice or event or simulat*)).mp.
17	budget impact.mp.
18	(multi criteria decision analysis or MCDA).mp.
19	(cost-effectiveness ratio or icer or CER).mp.
20	(economic* and model*).mp.
21	or/4-20
22	exp drug therapy/ or (drug$ or treatment$ or treated or treating or therapy or medication or medicine or medicinal or pharmaceutical or pharmaco-therapy or pharmacotherapy or pharmacological or therapeutic or pill or capsule or intravenous).ti,ab,hw,kw.
23	21 and 22
24	3 and 23
25	(case report or case series or woman or man or child or adolescent or female or male or boy or girl or infant).ti.
26	case reports/ or case study/ or case report$.jx. or case report$.jw.
27	(Ephemera or "Introductory Journal Article" or News or "Newspaper Article" or Editorial or Comment or Overall or Letter).pt. or in vitro Techniques/ or in vitro study/ or (commentary or editorial or comment or letter or mice or rat or mouse or animal or murine).ti.
28	review.pt. not (systematic or (meta and analy*) or ((indirect or mixed) and 'treatment comparison')).ti,ab.
29	exp guideline/ or (guideline or clinical protocol).ti,ab.
30	animal cell/ or "animal cell".mp. or animal experiment/ or "animal experiment".mp. or animal model/ or "animal model".mp. or cancer cell culture/ or "cancer cell culture".mp. or human cell/ or "human cell".mp. or human tissue/ or "human tissue".mp. or "in vitro study".mp. or nonhuman/ or "nonhuman".mp. or exp biological model/ or "biological model".mp. or exp cell culture/ or "cell culture".mp.
31	or/25-30
32	24 not 31
33	conference abstract.pt.
34	32 not 33
35	limit 24 to (conference abstract and yr="2020-current")

36	34 or 35
37	limit 36 to yr="2012-current"
38	exp systematic review/ or exp meta-analysis/ or (systematic or (meta and analy*) or ((indirect or mixed) and 'treatment comparison')).ti,ab.
39	limit 38 to yr="1883-2019"
40	37 not 39

Table 71 Search strategy for Medline

No.	Query
1	alzheimer*.ti,ab.
2	((mild* or early* or preclinical or pre-clinical) adj2 (cognitive impair* or cognitive dysfunction or cognitive decline)).ti,ab.
3	or/1-2
4	Cost-Benefit Analysis/ or Cost-Benefit Analysis.mp.
5	Costs and cost analysis/ or cost minimi?ation.mp.
6	economic evaluation.mp.
7	(cost effective* or CEA).mp.
8	(cost utilit* or CUA).mp.
9	Economics, Hospital/ or Economics/ or Economics, Nursing/ or Economics, Medical/ or Economics, Pharmaceutical/
10	(economic* or pharmacoeconomic* or (pharmaco adj1 economic*)).ti.
11	Monte carlo.mp.
12	decision tree.mp. or "decision tree"/
13	(decision adj3 (tree* or analys* or model*)).mp.
14	Models, Statistical/ or Markov Chains/ or (markov and (economic* or model*)).mp.
15	(patient adj2 simulat*).mp.
16	(discrete adj2 (choice or event or simulat*)).mp.
17	budget impact.mp.

18	(multi criteria decision analysis or MCDA).mp.
19	(cost-effectiveness ratio or icer or CER).mp.
20	(economic* and model*).mp.
21	or/4-20
22	exp drug therapy/ or (drug$ or treatment$ or treated or treating or therapy or medication or medicine or medicinal or pharmaceutical or pharmaco-therapy or pharmacotherapy or pharmacological or therapeutic or pill or capsule or intravenous).ti,ab,hw,kw.
23	21 and 22
24	3 and 23
25	(case report or case series or woman or man or child or adolescent or female or male or boy or girl or infant).ti.
26	case reports/ or case study/ or case report$.jw.
27	(Ephemera or "Introductory Journal Article" or News or "Newspaper Article" or Editorial or Comment or Overall or Letter).pt. or in vitro Techniques/ or in vitro study/ or (commentary or editorial or comment or letter or mice or rat or mouse or animal or murine).ti.
28	review.pt. not (systematic or (meta and analy*) or ((indirect or mixed) and 'treatment comparison')).ti,ab.
29	exp guideline/ or (guideline or clinical protocol).ti,ab.
30	animal cell/ or "animal cell".mp. or animal experiment/ or "animal experiment".mp. or animal model/ or "animal model".mp. or cancer cell culture/ or "cancer cell culture".mp. or human cell/ or "human cell".mp. or human tissue/ or "human tissue".mp. or "in vitro study".mp. or nonhuman/ or "nonhuman".mp. or exp biological model/ or "biological model".mp. or exp cell culture/ or "cell culture".mp.
31	or/25-30
32	24 not 31
33	limit 32 to yr="2012-current"
34	exp systematic review/ or exp meta-analysis/ or (systematic or (meta and analy*) or ((indirect or mixed) and 'treatment comparison')).ti,ab.
35	limit 34 to yr="1883-2019"
36	33 not 35

Table 72 Search strategy for Cochrane

No.	Query
1	alzheimer*.ti,ab.
2	((mild* or early* or preclinical or pre-clinical) adj2 (cognitive impair* or cognitive dysfunction or cognitive decline)).ti,ab.
3	or/1-2
4	Cost-Benefit Analysis/ or Cost-Benefit Analysis.mp.
5	Costs and cost analysis/ or cost minimi?ation.mp.
6	economic evaluation.mp.
7	(cost effective* or CEA).mp.
8	(cost utilit* or CUA).mp.
9	Economics, Hospital/ or Economics/ or Economics, Nursing/ or Economics, Medical/ or Economics, Pharmaceutical/
10	(economic* or pharmacoeconomic* or (pharmaco adj1 economic*)).ti.
11	Monte carlo.mp.
12	decision tree.mp. or "decision tree"/
13	(decision adj3 (tree* or analys* or model*)).mp.
14	Models, Statistical/ or Markov Chains/ or (markov and (economic* or model*)).mp.
15	(patient adj2 simulat*).mp.
16	(discrete adj2 (choice or event or simulat*)).mp.
17	budget impact.mp.
18	(multi criteria decision analysis or MCDA).mp.
19	(cost-effectiveness ratio or icer or CER).mp.
20	(economic* and model*).mp.
21	or/4-20
22	exp drug therapy/ or (drug$ or treatment$ or treated or treating or therapy or medication or medicine or medicinal or pharmaceutical or pharmaco-therapy or pharmacotherapy or pharmacological or therapeutic or pill or capsule or intravenous).ti,ab,hw,kw.
23	21 and 22

24	3 and 23
25	(case report or case series or woman or man or child or adolescent or female or male or boy or girl or infant).ti.
26	case reports/ or case study/ or case report$.jw.
27	(Ephemera or "Introductory Journal Article" or News or "Newspaper Article" or Editorial or Comment or Overall or Letter).pt. or in vitro Techniques/ or in vitro study/ or (commentary or editorial or comment or letter or mice or rat or mouse or animal or murine).ti.
28	review.pt. not (systematic or (meta and analy*) or ((indirect or mixed) and 'treatment comparison')).ti,ab.
29	exp guideline/ or (guideline or clinical protocol).ti,ab.
30	animal cell/ or "animal cell".mp. or animal experiment/ or "animal experiment".mp. or animal model/ or "animal model".mp. or cancer cell culture/ or "cancer cell culture".mp. or human cell/ or "human cell".mp. or human tissue/ or "human tissue".mp. or "in vitro study".mp. or nonhuman/ or "nonhuman".mp. or exp biological model/ or "biological model".mp. or exp cell culture/ or "cell culture".mp.
31	or/25-30
32	24 not 31
33	limit 32 to yr="2012-current"
34	exp systematic review/ or exp meta-analysis/ or (systematic or (meta and analy*) or ((indirect or mixed) and 'treatment comparison')).ti,ab.
35	limit 34 to yr="1883-2019"
36	33 not 35

Table 73 Search strategy for EconLit

No.	Query
1	(alzheimer* or ((mild* or early* or preclinical or pre-clinical) adj2 (cognitive impair* or cognitive dysfunction or cognitive decline))).mp.
2	Cost-Benefit Analysis.mp.
3	cost minimi?ation.mp.
4	economic evaluation.mp.
5	(cost effective* or CEA).mp.

6	(cost utilit* or CUA).mp.
7	(economic* or pharmacoeconomic* or (pharmaco adj1 economic*)).ti.
8	Monte carlo.mp.
9	decision tree.mp.
10	(decision adj3 (tree* or analys* or model*)).mp.
11	(markov and (economic* or model*)).mp.
12	(patient adj2 simulat*).mp.
13	(discrete adj2 (choice or event or simulat*)).mp.
14	budget impact.mp.
15	(multi criteria decision analysis or MCDA).mp.
16	(cost-effectiveness ratio or icer or CER).mp.
17	(economic* and model*).mp.
18	or/2-17
19	(drug$ or treatment$ or treated or treating or therapy or medication or medicine or medicinal or pharmaceutical or pharmaco-therapy or pharmacotherapy or pharmacological or therapeutic or pill or capsule or intravenous).mp.
20	18 and 19
21	1 and 20

Table 74 Search strategy for Database of Abstracts of Reviews of Effects

No.	Query
1	(alzheimer* or ((mild* or early* or preclinical or pre-clinical) adj2 (cognitive impair* or cognitive dysfunction or cognitive decline))).mp.
2	Cost-Benefit Analysis.mp.
3	cost minimi?ation.mp.
4	economic evaluation.mp.
5	(cost effective* or CEA).mp.
6	(cost utilit* or CUA).mp.

7	(economic* or pharmacoeconomic* or (pharmaco adj1 economic*)).ti.
8	Monte carlo.mp.
9	decision tree.mp.
10	(decision adj3 (tree* or analys* or model*)).mp.
11	(markov and (economic* or model*)).mp.
12	(patient adj2 simulat*).mp.
13	(discrete adj2 (choice or event or simulat*)).mp.
14	budget impact.mp.
15	(multi criteria decision analysis or MCDA).mp.
16	(cost-effectiveness ratio or icer or CER).mp.
17	(economic* and model*).mp.
18	or/2-17
19	(drug$ or treatment$ or treated or treating or therapy or medication or medicine or medicinal or pharmaceutical or pharmaco-therapy or pharmacotherapy or pharmacological or therapeutic or pill or capsule or intravenous).mp.
20	18 and 19
21	1 and 20

Table 75 Search strategy for NHS EED

No.	Query
1	(alzheimer* or ((mild* or early* or preclinical or pre-clinical) adj2 (cognitive impair* or cognitive dysfunction or cognitive decline))).mp.
2	Cost-Benefit Analysis.mp.
3	cost minimi?ation.mp.
4	economic evaluation.mp.
5	(cost effective* or CEA).mp.
6	(cost utilit* or CUA).mp.
7	(economic* or pharmacoeconomic* or (pharmaco adj1 economic*)).ti.

8	Monte carlo.mp.
9	decision tree.mp.
10	(decision adj3 (tree* or analys* or model*)).mp.
11	(markov and (economic* or model*)).mp.
12	(patient adj2 simulat*).mp.
13	(discrete adj2 (choice or event or simulat*)).mp.
14	budget impact.mp.
15	(multi criteria decision analysis or MCDA).mp.
16	(cost-effectiveness ratio or icer or CER).mp.
17	(economic* and model*).mp.
18	or/2-17
19	(drug$ or treatment$ or treated or treating or therapy or medication or medicine or medicinal or pharmaceutical or pharmaco-therapy or pharmacotherapy or pharmacological or therapeutic or pill or capsule or intravenous).mp.
20	18 and 19
21	1 and 20

Table 76 Search strategy for Interntaional HTA Database

No.	Query
1	((alzheimer* or "mild cognitive impair*") FROM 2012 TO 2022) AND (cost-benefit or cost-minimi* or cost-effective* or cost-util* or pharmacoeconomic* or pharmaco-economic* or monte carlo or decision tree* or markov or discrete or multi-criteria decision analysis or ICER or CER)

The database searches conducted on October 12, 2022 were limited to records published since 2012. The searches retrieved 1,398 records, of which 1,004 unique records were screened after removing duplicates. At the title and abstract screening level, 912 articles were excluded resulting in 92 articles retrieved for full-text review. Of those that progressed to the second round of review, 52 records were excluded hence, a total of 40 articles identified through the database searches were deemed to meet the PICOS criteria. No relevant studies were identified through the HTA website searches or the manual searches of conference proceedings, one record was identified through bibliography checks. Ultimately, 41 articles reporting on 34 unique economic evaluations were included in the review.

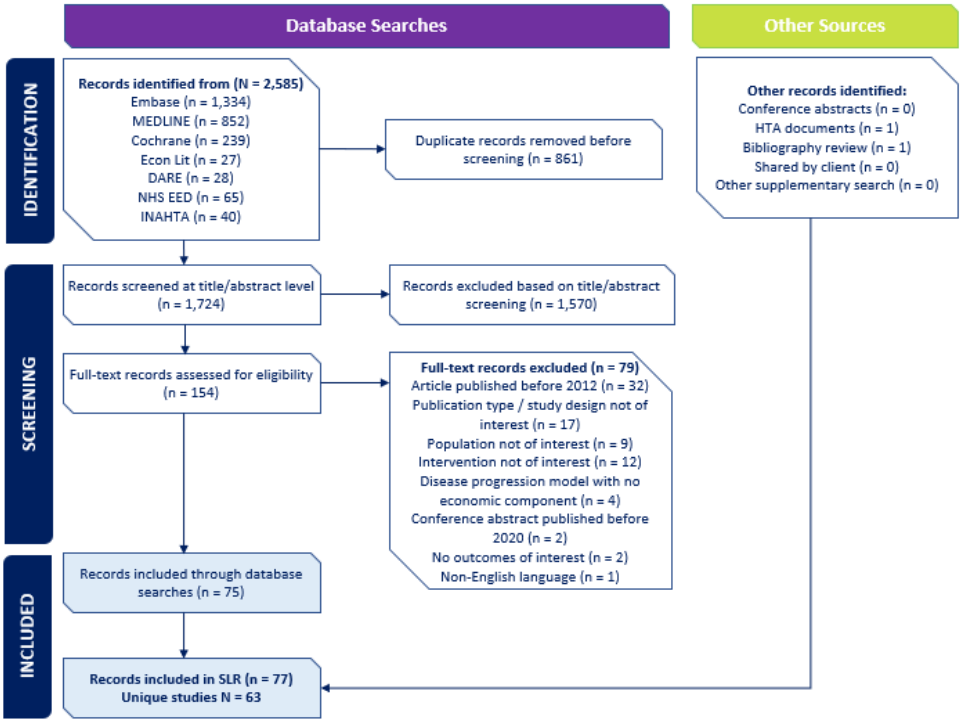
The literature searches were subsequently updated on September 4, 2023 and retrieved a total of 395 hits. Of these, 172 unique records remained after the removal of duplicate records retrieved from multiple databases and the removal of records identified by the October 2022 search. At the title and abstract screening level, 153 articles were excluded resulting in 19 articles retrieved for full-text review. Of those that progressed to the second round of review, 5 records were excluded hence, a total of 14 articles identified through the database searches were deemed to meet the PICOS criteria. One additional relevant study was identified through the HTA website searches. The search update yielded 15 new records for inclusion. When combined with the previous SLR (conducted on October 12, 2022), a total of 56 articles reporting on 47 unique economic evaluations were ultimately included in the review.

Another search update was conducted on June 25, 2025 and retrieved a total of 792 hits. Of these, 548 unique records remained after the removal of duplicate records retrieved from multiple databases and the removal of records identified by the previous searches. At the title and abstract screening level, 505 articles were excluded resulting in 43 articles retrieved for full-text review. Of those that progressed to the second round of review, 22 records were excluded hence, a total of 21 articles identified through the database searches were deemed to meet the PICOS criteria. No further articles of interest were identified through the grey literature searches. When combined with the previous SLR updates, a total of 77 articles reporting on 63 unique economic evaluations were ultimately included in the review. Figure 21 summarizes the flow of studies, identified by the 2022, 2023, and 2025 searches, through the screening process, from the initial search hits to the final number of included studies in the SLR.

The evidence base includes 30 unique economic evaluations which evaluated **the cost-effectiveness of cholinesterase inhibitors, memantine, aducanumab, lecanemab and donanemab for the treatment of Alzheimer's disease using cost utility methods. Nine** further studies leveraged economic models to perform other types of costing analyses including, budget impact analyses and cost of illness analyses (153-161).

In addition, the SLR identified 24 economic models based on hypothetical disease-modifying therapies (DMTs). These publications were frameworks developed to evaluate cost-effectiveness or to perform value based pricing analyses for hypothetical DMTs which represent the kind of novel Alzheimer's disease treatments that could be licensed in the future (35, 143, 162-178). Although these publications are not assessing real therapies, they may offer important insights into both modelling methods and the potential economic value of future therapies. The below sections therefore provide separate results for hypothetical models.

Figure 21 PRISMA Diagram Economic Evaluations Search (Literature Search Conducted October 2022 and Updated in September 2023 and June 2025)



Abbreviations: DARE = Database Of Abstracts of Reviews of Effects; HTA = health technology assessment; INAHTA = International HTA Database; NHS EED = National Health Service Economic Evaluation Database; SLR = systematic literature review

Research question 1 identified one search result that is included in the model and is presented in Table 77.

Table 77 Literature search results included in the model

Sköldunger, 2013 (143)	Dementia diagnosis was based on DSM-IV while states and progression were defined according to the MMSE. It was assumed that in 2005 (the year of the model) 100,000 persons had MCI-AD in Sweden. Two population-based studies of people aged >75 years were used as empirical cores for the model.	Study Objective: To present a hypothetical economic model of DMT in AD. Currency (Year): SEK (NR) Type of model: Markov model Perspective: Sweden societal perspective Time Horizon: 20 years Cycle length: 1 year Health States: MCI-AD, mild AD (18 ≥MMSE ≤23), moderate AD (10 ≥MMSE ≤17), severe AD (0 ≥MMSE ≤9), and death Discounting: 3.0% for both cost and benefits Cost/ resource input types and data source: Long-term institutional care, hospital care, hospital clinic visits, day care, home services and informal care costs. Wimo 2007 (179), Wimo 2009 (180), and Wimo 2010 (181)

Efficacy data source(s): NA

Utility data source(s): Ekman 2007 (182)

Abbreviations: AD, Alzheimer's disease; DMT, Disease Modifying Therapy; MMSE, Mini Mental State Exam; NR, not reported.

In addition, another meta-analysis by Landeiro et al. (2020) (8) was used in the model. It was not identified as a separate publication through research question described above but was used as utility source in several publications that were identified in this search.

Table 78 Literature search results included in the model as utility source

Study Name	Geography	Study Design and Recruitment	Data Source/ Number of Centers	Intervention and Comparator Groups Studied	Respondents	Description of the AD Population Evaluated	Response Rate (%)	Sample Size	Health States Evaluated
Landeiro et al. (2020) (8)	Canada, Sweden, Norway, Denmark, Finland, Germany, UK, France, Spain, Hungary, Japan, Netherlands, Russia, Taiwan, US, Austria	SLR N/A	Published studies	N/A	General Public	People with predementia AD, MCI or dementia	NR	58 studies	**Patient's utilities** Patients with MCI Patients with MCI or dementia Patients mild and/or moderate disease severity

Health-related quality of life: Research question 2

Objective of literature search: What evidence is available on utilities associated with Alzheimer's disease across the continuum of disease (i.e., from MCI-AD through to severe dementia due to Alzheimer's disease)?

Source: see sources in Research question 1.

The inclusion and exclusion criteria outlined in Research question 1 (Section I.1.1) were applied in the same manner to the present question.

Table 79 Search strategy for Embase

No.	Query	Results
1	alzheimer*.ti,ab.	NR
2	((mild* or early* or preclinical or pre-clinical) adj2 (cognitive impair* or cognitive dysfunction or cognitive decline)).ti,ab.	NR
3	1 or 2	NR
4	(Quality of Life in Alzheimer's Disease or QoL-AD).mp.	NR
5	(dementia quality of life or DEMQOL).mp.	NR
6	(EQ5D or EQ-5D or EuroQoL).mp.	NR
7	(medical outcome study or short-form or shortform or mos-sf or sf12 or sf 12 or sf16 or sf 16 or sf20 or sf 20 or sf36 or sf 36 or sf6d or sf 6d or RAND36 or RAND12 or RAND 36 or RAND 12).mp.	NR
8	(icepop or icecap* or duke health profile or dhp or core outcome measure? or core om).ti,ab.	NR
9	(health utility index or health utility index or HUI2 or HUI3 or HUI 2 or HUI 3 or aaiqol or aai-qol or cdqlp or qolas or qolad or qol-ad or qold or dqol 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).mp.	NR
10	(modified coop* or modified wonca* or "psychological well-being in cognitively impaired persons").ti,ab.	NR
11	(Time Trade Off or Standard Gamble or utility index$ or visual analog* or rating$ scale).mp.	NR
12	(health state* or HSUV).mp.	NR
13	patient preference.mp. or exp Patient Preference/	NR

No.	Query	Results
14	exp care partner burden/	NR
15	exp care partner strain index/	NR
16	exp care partner support/	NR
17	(care partner burden or care partner strain or care partner support).mp.	NR
18	(Utilit* or disutilit*).mp.	NR
19	Quality of life.mp. or exp "quality of life"/ or exp health status/	NR
20	18 and 19	NR
21	or/4-17,20	NR
22	3 and 21	NR
23	(case report or case series or woman or man or child or adolescent or female or male or boy or girl or infant).ti.	NR
24	case reports/ or case study/ or case report$.jx. or case report$.jw.	NR
25	(Ephemera or "Introductory Journal Article" or News or "Newspaper Article" or Editorial or Comment or Overall).pt. or in vitro Techniques/ or in vitro study/ or (commentary or editorial or comment or letter or mice or rat or mouse or animal or murine).ti.	NR
26	review.pt. not (systematic or (meta and analy*) or ((indirect or mixed) and 'treatment comparison')).ti,ab.	NR
27	exp practice guideline/ or (guideline or clinical protocol).ti,ab.	NR
28	animal cell/ or "animal cell".mp. or animal experiment/ or "animal experiment".mp. or animal model/ or "animal model".mp. or cancer cell culture/ or "cancer cell culture".mp. or human cell/ or "human cell".mp. or human tissue/ or "human tissue".mp. or "in vitro study".mp. or nonhuman/ or "nonhuman".mp. or exp biological model/ or "biological model".mp. or exp cell culture/ or "cell culture".mp.	NR
29	exp clinical trial/ or exp randomized controlled trial/ or trial$.mp. or phase 1.mp. or phase 2.mp. or phase 3.mp. or phase 4.mp. or phase i.mp. or phase ii.mp. or phase iii.mp. or phase iv.mp. or ex-vivo.mp. or pharmacokinetics.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword heading word, floating subheading word, candidate term word]	NR
30	or/23-29	NR
31	22 not 30	NR

No.	Query	Results
32	conference abstract.pt.	NR
33	31 not 32	NR
34	limit 31 to (conference abstract and yr="2020-current")	NR
35	33 or 34	NR
36	limit 35 to yr="2012 -Current"	NR
37	exp systematic review/ or exp meta-analysis/ or (systematic or (meta and analy*) or ((indirect or mixed) and 'treatment comparison')).ti,ab.	NR
38	limit 37 to yr="1883 - 2019"	NR
39	36 not 38	NR

Table 80 Search strategy for Medline

No.	Query	Results
1	alzheimer*.ti,ab.	NR
2	((mild* or early* or preclinical or pre-clinical) adj2 (cognitive impair* or cognitive dysfunction or cognitive decline)).ti,ab.	NR
3	1 or 2	NR
4	(Quality of Life in Alzheimer's Disease or QOL-AD).mp.	NR
5	(dementia quality of life or DEMQOL).mp.	NR
6	(EQ5D or EQ-5D or EuroQoL).mp.	NR
7	(medical outcome study or short-form or shortform or mos-sf or sf12 or sf 12 or sf16 or sf 16 or sf20 or sf 20 or sf36 or sf 36 or sf6d or sf 6d or RAND36 or RAND12 or RAND 36 or RAND 12).mp.	NR
8	(icepop or icecap* or duke health profile or dhp or core outcome measure? or core om).ti,ab.	NR
9	(health utility index or health utility index or HUI2 or HUI3 or HUI 2 or HUI 3 or aaiqol or aai-qol or cdqlp or qolas or qolad or qol-ad or qold or dqol 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).mp.	NR

No.	Query	Results
10	(modified coop* or modified wonca* or "psychological well-being in cognitively impaired persons").ti,ab.	NR
11	(Time Trade Off or Standard Gamble or utility index$ or visual analog* or rating$ scale).mp.	NR
12	(health state* or HSUV).mp.	NR
13	patient preference.mp. or exp Patient Preference/	NR
14	exp care partner burden/	NR
15	(care partner burden or care partner strain or care partner support).mp.	NR
16	(Utilit* or disutilit*).mp.	NR
17	Quality of life.mp. or exp "quality of life"/ or exp health status/	NR
18	16 and 17	NR
19	or/4-15,18	NR
20	3 and 19	NR
21	(case report or case series or woman or man or child or adolescent or female or male or boy or girl or infant).ti.	NR
22	case reports/ or case study/ or case report$.jw.	NR
23	(Ephemera or "Introductory Journal Article" or News or "Newspaper Article" or Editorial or Comment or Overall).pt. or in vitro Techniques/ or in vitro study/ or (commentary or editorial or comment or letter or mice or rat or mouse or animal or murine).ti.	NR
24	review.pt. not (systematic or (meta and analy*) or ((indirect or mixed) and 'treatment comparison')).ti,ab.	NR
25	exp practice guideline/ or (guideline or clinical protocol).ti,ab.	NR
26	animal cell/ or "animal cell".mp. or animal experiment/ or "animal experiment".mp. or animal model/ or "animal model".mp. or cancer cell culture/ or "cancer cell culture".mp. or human cell/ or "human cell".mp. or human tissue/ or "human tissue".mp. or "in vitro study".mp. or nonhuman/ or "nonhuman".mp. or exp biological model/ or "biological model".mp. or exp cell culture/ or "cell culture".mp.	NR
27	exp clinical trial/ or exp randomized controlled trial/ or trial$.mp. or phase 1.mp. or phase 2.mp. or phase 3.mp. or phase 4.mp. or phase i.mp. or phase ii.mp. or phase iii.mp. or phase iv.mp. or ex-vivo.mp. or pharmacokinetics.mp. [mp=title, book title, abstract, original title, name of substance word, subject heading word, floating sub-heading word,	NR

No.	Query	Results
	keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	
28	or/21-27	NR
29	20 not 28	NR
30	limit 29 to yr="2012 -Current"	NR

Table 81 Search strategy for Cochrane

No.	Query	Results
1	alzheimer*.ti,ab.	NR
2	((mild* or early* or preclinical or pre-clinical) adj2 (cognitive impair* or cognitive dysfunction or cognitive decline)).ti,ab.	NR
3	1 or 2	NR
4	(Quality of Life in Alzheimer's Disease or QOL-AD).mp.	NR
5	(dementia quality of life or DEMQOL).mp.	NR
6	(EQ5D or EQ-5D or EuroQoL).mp.	NR
7	(medical outcome study or short-form or shortform or mos-sf or sf12 or sf 12 or sf16 or sf 16 or sf20 or sf 20 or sf36 or sf 36 or sf6d or sf 6d or RAND36 or RAND12 or RAND 36 or RAND 12).mp.	NR
8	(icepop or icecap* or duke health profile or dhp or core outcome measure? or core om).ti,ab.	NR
9	(health utility index or health utility index or HUI2 or HUI3 or HUI 2 or HUI 3 or aaiqol or aai-qol or cdqlp or qolas or qolad or qol-ad or qold or dqol 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).mp.	NR
10	(modified coop* or modified wonca* or "psychological well-being in cognitively impaired persons").ti,ab.	NR
11	(Time Trade Off or Standard Gamble or utility index$ or visual analog* or rating$ scale).mp.	NR
12	(health state* or HSUV).mp.	NR

No.	Query	Results
13	patient preference.mp. or exp Patient Preference/	NR
14	exp care partner burden/	NR
15	(care partner burden or care partner strain or care partner support).mp.	NR
16	(Utilit* or disutilit*).mp.	NR
17	Quality of life.mp. or exp "quality of life"/ or exp health status/	NR
18	16 and 17	NR
19	or/4-15,18	NR
20	3 and 19	NR
21	(case report or case series or woman or man or child or adolescent or female or male or boy or girl or infant).ti.	NR
22	case reports/ or case study/ or case report$.jw.	NR
23	(Ephemera or "Introductory Journal Article" or News or "Newspaper Article" or Editorial or Comment or Overall).pt. or in vitro Techniques/ or in vitro study/ or (commentary or editorial or comment or letter or mice or rat or mouse or animal or murine).ti.	NR
24	review.pt. not (systematic or (meta and analy*) or ((indirect or mixed) and 'treatment comparison')).ti,ab.	NR
25	exp practice guideline/ or (guideline or clinical protocol).ti,ab.	NR
26	animal cell/ or "animal cell".mp. or animal experiment/ or "animal experiment".mp. or animal model/ or "animal model".mp. or cancer cell culture/ or "cancer cell culture".mp. or human cell/ or "human cell".mp. or human tissue/ or "human tissue".mp. or "in vitro study".mp. or nonhuman/ or "nonhuman".mp. or exp biological model/ or "biological model".mp. or exp cell culture/ or "cell culture".mp.	NR
27	exp clinical trial/ or exp randomized controlled trial/ or trial$.mp. or phase 1.mp. or phase 2.mp. or phase 3.mp. or phase 4.mp. or phase i.mp. or phase ii.mp. or phase iii.mp. or phase iv.mp. or ex-vivo.mp. or pharmacokinetics.mp. [mp=title, original title, abstract, floating sub-heading word, mesh headings, heading words, keyword]	NR
28	or/21-27	NR
29	20 not 28	NR
30	limit 29 to yr="2012 -Current"	NR

Table 82 Search strategy for EconLit

No.	Query	Results
1	(alzheimer* or ((mild* or early* or preclinical or pre-clinical) adj2 (cognitive impair* or cognitive dysfunction or cognitive decline))).mp.	NR
2	(Quality of Life in Alzheimer's Disease or QOL-AD).mp.	NR
3	(dementia quality of life or DEMQOL).mp.	NR
4	(EQ5D or EQ-5D or EuroQoL).mp.	NR
5	(medical outcome study or short-form or shortform or mos-sf or sf12 or sf 12 or sf16 or sf 16 or sf20 or sf 20 or sf36 or sf 36 or sf6d or sf 6d or RAND36 or RAND12 or RAND 36 or RAND 12).mp.	NR
6	(icepop or icecap* or duke health profile or dhp or core outcome measure? or core om).mp.	NR
7	(health utility index or health utility index or HUI2 or HUI3 or HUI 2 or HUI 3 or aaiqol or aai-qol or cdqlp or qolas or qolad or qol-ad or qold or dqol 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).mp.	NR
8	(modified coop* or modified wonca* or "psychological well-being in cognitively impaired persons").mp.	NR
9	(Time Trade Off or Standard Gamble or utility index$ or visual analog* or rating$ scale).mp.	NR
10	(health state* or HSUV).mp.	NR
11	patient preference.mp.	NR
12	(care partner burden or care partner strain or care partner support).mp.	NR
13	(Utilit* or disutilit*).mp.	NR
14	Quality of life.mp.	NR
15	13 and 14	NR
16	or/2-12,15	NR
17	1 and 16	NR
18	limit 17 to yr="2012 -Current"	NR

Table 83 Search strategy for Database of Abstracts of Reviews of Effects

No.	Query	Results
1	(alzheimer* or ((mild* or early* or preclinical or pre-clinical) adj2 (cognitive impair* or cognitive dysfunction or cognitive decline))).mp.	NR
2	(Quality of Life in Alzheimer's Disease or QOL-AD).mp.	NR
3	(dementia quality of life or DEMQOL).mp.	NR
4	(EQ5D or EQ-5D or EuroQoL).mp.	NR
5	(medical outcome study or short-form or shortform or mos-sf or sf12 or sf 12 or sf16 or sf 16 or sf20 or sf 20 or sf36 or sf 36 or sf6d or sf 6d or RAND36 or RAND12 or RAND 36 or RAND 12).mp.	NR
6	(icepop or icecap* or duke health profile or dhp or core outcome measure? or core om).mp.	NR
7	(health utility index or health utility index or HUI2 or HUI3 or HUI 2 or HUI 3 or aaiqol or aai-qol or cdqlp or qolas or qolad or qol-ad or qold or dqol 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).mp.	NR
8	(modified coop* or modified wonca* or "psychological well-being in cognitively impaired persons").mp.	NR
9	(Time Trade Off or Standard Gamble or utility index$ or visual analog* or rating$ scale).mp.	NR
10	(health state* or HSUV).mp.	NR
11	patient preference.mp.	NR
12	(care partner burden or care partner strain or care partner support).mp.	NR
13	(Utilit* or disutilit*).mp.	NR
14	Quality of life.mp.	NR
15	13 and 14	NR
16	or/2-12,15	NR
17	1 and 16	NR

Table 84 Search strategy for NHS EED

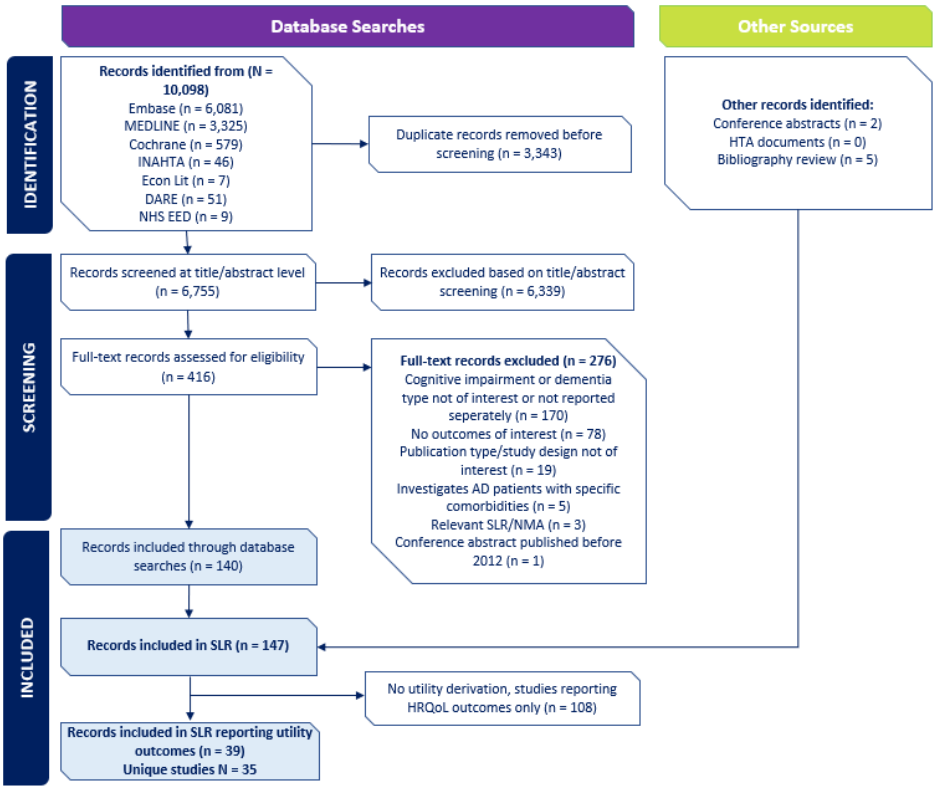
No.	Query	Results
1	(alzheimer* or ((mild* or early* or preclinical or pre-clinical) adj2 (cognitive impair* or cognitive dysfunction or cognitive decline))).mp.	NR
2	(Quality of Life in Alzheimer's Disease or QOL-AD).mp.	NR
3	(dementia quality of life or DEMQOL).mp.	NR
4	(EQ5D or EQ-5D or EuroQoL).mp.	NR
5	(medical outcome study or short-form or shortform or mos-sf or sf12 or sf 12 or sf16 or sf 16 or sf20 or sf 20 or sf36 or sf 36 or sf6d or sf 6d or RAND36 or RAND12 or RAND 36 or RAND 12).mp.	NR
6	(icepop or icecap* or duke health profile or dhp or core outcome measure? or core om).mp.	NR
7	(health utility index or health utility index or HUI2 or HUI3 or HUI 2 or HUI 3 or aaiqol or aai-qol or cdqlp or qolas or qolad or qol-ad or qold or dqol 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).mp.	NR
8	(modified coop* or modified wonca* or "psychological well-being in cognitively impaired persons").mp.	NR
9	(Time Trade Off or Standard Gamble or utility index$ or visual analog* or rating$ scale).mp.	NR
10	(health state* or HSUV).mp.	NR
11	patient preference.mp.	NR
12	(care partner burden or care partner strain or care partner support).mp.	NR
13	(Utilit* or disutilit*).mp.	NR
14	Quality of life.mp.	NR
15	13 and 14	NR
16	or/2-12,15	NR
17	1 and 16	NR
18	limit 17 to yr="2012 -Current"	NR

The database searches conducted on September 14, 2022 were limited to records published since 2012. The searches identified 6,008 records, of which 4,215 unique records were screened after removing duplicates. At the title and abstract screening level, 3,890 articles were excluded resulting in 325 articles retrieved for full-text review. Of those that progressed to the second round of review, 210 records were excluded hence, a total of 115 articles identified through the database searches were deemed to meet the PICOS criteria. Five further studies were identified through bibliography checks and one additional study was identified through manual searches of conference proceedings. Ultimately, 121 articles reporting on 102 unique studies were included in the review.

The literature searches were subsequently updated on September 4, 2023 and retrieved a total of 1,638 hits. Of these, 677 unique records remained after the removal of duplicate records retrieved from multiple databases and the removal of records identified by the September 2022 search. At the title and abstract screening level, 657 articles were excluded resulting in 20 articles retrieved for full-text review. Of those that progressed to the second round of review, 13 records were excluded hence, a total of seven articles identified through the database searches were deemed to meet the PICOS criteria. One additional relevant study was identified through the hand searching of conference proceedings. The search update yielded 7 new records for inclusion. When combined with the previous SLR (conducted on September 14, 2022), a total of 129 articles met the PICOS criteria. Of the 129 includes, 34 publications reporting on 30 unique studies derived utility estimates for Alzheimer's populations.

Another search update was conducted on June 25, 2025 and retrieved a total of 2,452 hits. Of these, 1,863 unique records remained after the removal of duplicate records retrieved from multiple databases and the removal of records identified by the previous searches. At the title and abstract screening level, 1,792 articles were excluded resulting in 71 articles retrieved for full-text review. Of those that progressed to the second round of review, 53 records were excluded hence, a total of 18 articles identified through the database searches were deemed to meet the PICOS criteria. No further articles of interest were identified through the grey literature searches. When combined with the previous SLRs, a total of 147 articles met the PICOS criteria. As shown in Figure 22, 39 publications reporting on 35 unique studies derived utility estimates for Alzheimer's populations, the remainder reported only HRQoL outcomes.

Figure 22 PRISMA Diagram Utilities Search (Literature Search Conducted September 2022 and Updated in September 2023 and June 2025)



Out of the 35 studies that were identified in the SLR, the results of 2 studies (for caregiver utilities; Belger et al and Matza et al) deemed relevant and are included in the model.

Literature search results included in the model are presented in Table 85.

Table 85 Literature search results included in the model

Study Name	Geography	Study Design and Recruitment	Data Source/ Number of Centers	Intervention and Comparator Groups Studied	Respondents	Description of the AD Population Evaluated	Response Rate (%)	Sample Size	Health States Evaluated
Belger et al., 2022 (136)	UK	Time trade-off study Other	NR	N/A	General Public	Mild, moderate, or severe	NR	109	**Care partner utilities** Care partners living with patients with mild AD Care partners living with patients with moderate AD Care partners living with patients with severe AD Care partners living separately from patients with mild AD Care partners living separately from patients with moderate AD Care partners of persons with severe AD cared for in a nursing home
Matza et al., 2024 (135)	UK, US	Time trade-off study Convenience sample	Alzheimer's Europe	N/A	General Public	Patients with MCI and dementia due to AD	NR	506	**Care partner utilities** Care partners (child or spouse) living with patients with MCI

	Care partners (child or spouse) living with patients with mild AD
	Care partners (child or spouse) living with patients with moderate AD

Abbreviations: AD, Alzheimer's Disease; N/A, not applicable; NR, not reported

I.1.2 Quality assessment and generalizability of estimates

Quality assessment of the included economic evaluations was conducted using the 36-item Drummond checklist (183). This checklist summarizes how well each study meets criteria across three categories: study design, data collection, and analysis and interpretation of results. No overall score was assigned with this tool, but rather the answers to questions relevant to each domain were assigned as 'Yes,' 'No,' 'Not clear,' or 'Not appropriate'. Only studies available in full-text were assessed for quality due to lack of details available for assessment from abstracts and posters.

I.1.3 Unpublished data

Not applicable.

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

J.1 External literature for input to the health economic model

Literature informing some model assumptions/inputs relevant for the Danish context using targeted search approaches complemented the systematic database search (economic SLR, with the objective to identify economic evaluations, utility values, resource utilization and cost evidence that may be leveraged to inform the development of a CEM for donanemab for the treatment of early symptomatic AD, and the selection of model inputs, to support future HTA submissions, was updated in June 2025 and can be provided upon request).

J.1.1 Targeted literature search for resource use costs in MCI and mild AD in the Nordic setting

The aim of this targeted search in PubMed was to identify costs of resource use in MCI and mild AD, differentiated by severity stages and specific for either Danish or Nordic setting. Due to the known variation across single studies, we did not want evidence from such, thus limited our research to meta-analyses or SLRs. Moreover, we wanted recent evidence and therefore limited the search to five most recent years.

Table 86 Sources included in the targeted literature search

Source name/ database	Location/source	Search strategy	Date of search
PubMed	https://pubmed.ncbi.nlm.nih.gov/	Advanced search: **(alzheimer* OR dementia) AND (severity) AND (cost) AND (Denmark OR Nordic)** Filters: **in the last 5 years, Meta-Analysis, Review, Systematic Review**	2025-09-20

This search resulted in two hits:

1. Jönsson et al. The Costs of Dementia in Europe: An Updated Review and Meta-analysis.

2. Frederiksen et al. A Literature Review on the Burden of Alzheimer's Disease on Care Partners.

The first hit was deemed most relevant as it included costs from several regions, including specifically for the Nordic markets, and included both direct health care costs, cost of institutionalization and community care as well as caregiver costs. Whereas the second hit was specific for data on caregivers. However, the meta-analysis did not include data on MCI patients, so an assumption had to be made on how high the cost burden of those patients is in relation to mild AD patients. In the economic SLR an economic evaluation on Swedish data (Sköldunger et al 2013) was extracted as part of 'Cost Utility Frameworks and Value Based Pricing Analyses for Hypothetical Alzheimer's disease Therapies' which showed costs stratified by health states from MCI to severe; the proportion of costs in MCI in relation to mild AD was 56 %. Thus, in the model input for resource use costs for MCI, we used the same proportion but in relation to the data presented in Jönsson et al.

J.1.2 Targeted literature search for caregiver characteristics in the Nordic setting

The aim of this targeted search was to identify the caregiver characteristics, age and proportion male/female in MCI or mild AD patients specific for the Nordic setting. We wanted recent evidence and therefore limited the search to five most recent years.

Table 87 Sources included in the targeted literature search

Source name/ database	Location/source	Search strategy	Date of search
PubMed	https://pubmed.ncbi.nlm.nih.gov/	Advanced search: **(Alzheimer* OR dementia) AND (descriptive data) AND (carer OR caregiver OR spouse OR non-spouse) AND (Denmark OR Sweden OR Finland OR Norway)** Filters: **in the last 5 years**	2025-01-02

Abbreviations:

The search yielded 31 hits of which a Swedish study by Johansson et al from 2021 included all the information we needed for caregiver characteristics (caregivers per patient, proportion of child caregivers, mean age of child caregivers, proportion of child caregivers that were females, proportion of spouse caregivers, mean age of spouse caregivers, proportion of spouse caregivers that were females), thus it was chosen to inform these assumptions in the model. The data was considered relevant for the Danish setting.

Appendix K. Composition of best supportive care

Table 88 summarizes information on the available best supportive care for AD patients in Danish clinical practice.

Table 88 Information on best supportive care for AD patients

Overview of comparator	AChEI			Memantine
Generic name	**Donepezil**	**Rivastigmine**	**Galantamine**	**Memantine**
ATC code	N06DA02	N06DA03	N06DA04	N06DX01
Mechanism of action	Donepezil hydrochloride is a specific and reversible inhibitor of acetylcholinesterase, the predominant cholinesterase in the brain. Donepezil hydrochloride is in vitro an over 1,000-fold more potent inhibitor of this enzyme than of butyrylcholinesterase, an enzyme that occurs mainly outside the central nervous system.	Rivastigmine is a carbamate-type acetyl- and butyrylcholinesterase inhibitor, which is thought to facilitate cholinergic nerve transmission by delaying the breakdown of acetylcholine released by functionally intact cholinergic neurons.	Galantamine, a tertiary alkaloid, is a selective, competitive and reversible inhibitor of acetylcholinesterase. Galantamine also enhances acetylcholine's own effect on nicotinic receptors, probably by binding to an allosteric binding site on the receptor. As a result, an increased activity of the cholinergic system can be obtained in patients with dementia of the Alzheimer type, associated with improved cognitive function.	There is increasing evidence that dysfunction of glutamatergic neurotransmission, particularly at NMDA receptors, contributes to both the appearance of symptoms and disease progression in neurodegenerative dementia. Memantine is a voltage-dependent non- competitive moderate affinity NMDA receptor antagonist. It modulates the effects of pathologically elevated tonic glutamate levels that can lead to neuronal dysfunction.

Overview of comparator	AChEI			Memantine
Method of administration	Donepezil should be taken orally, in the evening, just prior to retiring. In case of sleep disturbances including abnormal dreams, nightmares or insomnia intake of donepezil in the morning may be considered.	Rivastigmine should be administered twice a day, with morning and evening meals. The capsules should be swallowed whole.	Galantamine extended-release capsules should be given orally once a day in the morning, preferably with a meal. The capsules are swallowed whole (do not chew or crush) together with liquid. For patients who have difficulty swallowing, the capsule contents can be emptied and swallowed whole with liquid. The capsule contents (matrix tablets) must not be chewed or crushed.	Marbodin should be administered once daily and should be taken at the same time each day. The film-coated tablets can be taken with or without food.

Overview of comparator	AChEI			Memantine
Dosing	Treatment begins with 5 mg/day (dose once a day). A dose of 5 mg/day should be maintained for at least one month to allow assessment of the earliest clinical responses and to achieve a steady-state concentration of donepezil hydrochloride. After one month of clinical assessment with a dosage of 5 mg/day, the dose of donepezil can be increased to 10 mg/day (dosage once a day). The maximum recommended daily dose is 10 mg. Doses exceeding 10 mg/day have not been studied in clinical trials.	The starting dose is 1.5 mg twice daily. If this dose is well tolerated after at least two weeks of treatment, the dose can be increased to 3 mg twice daily. Subsequent dose increases to 4.5 and later to 6 mg twice daily should also be based on how well previous dose levels were tolerated and should only be considered after at least two weeks of treatment at the previous dose level.	The recommended starting dose is 8 mg daily for 4 weeks. The initial maintenance dose is 16 mg daily and the patient must stay on 16 mg daily for at least 4 weeks. An increase to the maintenance dose of 24 mg daily should be considered on an individual basis after evaluation of treatment, including assessment of therapeutic benefit and tolerability.	The maximum daily dose is 20 mg per day. To reduce the risk of side effects, the maintenance dose is achieved by a titration increase of 5 mg per week during the first 3 weeks as follows. Other tablet strengths are available for up titration.
Dosing in the health economic model (including relative dose intensity)	10 mg/day	Not in model	Not in model	20 mg/day
Should the medicine be administered with other medicines?	No	No	No	No

Overview of comparator	AChEI			Memantine
Treatment duration/ criteria for end of treatment	Maintenance treatment can continue as long as there is therapeutic benefit for the patient. Therefore, the clinical utility of donepezil should be regularly evaluated. When evidence of therapeutic effect is no longer available, discontinuation of treatment should be considered.	Maintenance treatment can continue as long as the patient has a favorable effect of the treatment. Therefore, the clinical benefit of rivastigmine should be monitored regularly, especially for patients treated with doses lower than 3 mg twice daily. If, after 3 months of dosing, the maintenance treatment has not given the patient a beneficial development of dementia symptoms, the treatment must be discontinued. Discontinuation should also be considered when therapeutic effect is no longer present.	Maintenance treatment can continue as long as the treatment effect is favorable, and the patient tolerates the treatment with galantamine.	Maintenance treatment can continue as long as the treatment effect is favorable, and the patient tolerates treatment with memantine. Discontinuation of memantine should be considered when the treatment effect is no longer achieved or when the patient does not tolerate the treatment.

Overview of comparator	AChEI			Memantine
Need for diagnostics or other tests (i.e. companion diagnostics)	Diagnosis should be made according to accepted guidelines (e.g. DSM IV, ICD 10). Therapy with donepezil should only be started if a caregiver is available who will regularly monitor drug intake for the patient.	Diagnosis must be made in accordance with current guidelines. Treatment with rivastigmine should only be started if a healthcare provider is available who can monitor the patient's medication continuously.	The diagnosis of probable dementia of the Alzheimer type must be established in accordance with current clinical guidelines.	Treatment must be initiated and supervised by a physician experienced in the diagnosis and treatment of Alzheimer's dementia. The therapy should only be started if there is a caregiver who regularly monitors the patient's medication intake. Diagnosis should be made according to current guidelines. The tolerability and dosage of memantine should be regularly evaluated, preferably within three months of starting treatment. Thereafter, the clinical benefit and the patient's tolerability should be regularly evaluated according to current guidelines.
Package size(s)	98 tablets/package	112 capsules/package	84 capsules/package	98 tablets/package

Abbreviations: mg, milligram; NMDA, N-methyl-D-aspartate.

Source: SmPC donepezil (184), SmPC rivastigmine (185), SmPC galantamine (186), SmPC memantine (187).

Appendix L. Table on treatment completion scenarios

Table 89 Completion Scenarios Used Within the Model

	Discontinuation Rule	Base Case
Positive stopping rule	Due to treatment duration of 18-months. Due to amyloid clearance at month 12 defined as <24.1 CL assessed by amyloid PET scan.	The treatment effect is calculated based on the following assumptions: • **Within TB2 trial (18 months):** full treatment effect of donanemab applied in the model (HR 0.62 [95% CI 0. 494, 0. 779]) for the 18-month period whether treatment is completed early on confirmed amyloid clearance at month 12 or continued to the 18-month maximum without clearance: ✓ Following the SmPC stopping rule, 69.7% (65.45, 73.55) of patients in the EU eligible population achieved amyloid plaque clearance at Week 52 in TB2 and therefore complete treatment at 12 months, in line with the TB2 trial design (188). ✓ All the remaining patients completed treatment at 18 months • **Post-trial (medium-term):** full treatment effect is retained for 4.5 years until patients have accumulated amyloid up to 'positive' level. ✓ The mean amyloid level with the treatment of donanemab at 18-month is 12.67 CL (128). ✓ The threshold for amyloid positivity is 24.1 CL, > 24.1 CL equates to the existence of amyloid pathology (107) ✓ The re-accumulation rate of amyloid plaque is 2.4 CL (108) ✓ 4.5 years are then calculated based on the above evidence [(24.1-12.67)/2.4≈4.8 years] ✓ Linear increase of the amyloid level over time is assumed Hence, the base case assumes that full treatment effect would then be retained until Year 6. • **Post-trial (long-term):** treatment effect gradually wanes to zero (i.e. the hazard ratio of progression becomes 1) over a further period of 11 years until the amyloid level accumulates up to 'downstream clinical meaningful progression' level.

		✓ The threshold for 'downstream clinical meaningful progression' amyloid level is 50 CL (125, 126). Amyloid level below this threshold is not considered as a clinical meaningful impact on cognitive impairment and not associated with an increased risk of clinical progression ✓ The re-accumulation rate of amyloid plaque is 2.4 CL (108) ✓ 11 years are then calculated based on the above evidence [(50-24.1)/2.4≈11 years] ✓ Linear increase of the amyloid level over time is assumed Hence, the base case assumes that treatment effect warns to zero after Year 17.
Negative stopping rule	Discontinuation due to progression to moderate AD dementia.	Patients who discontinue due to progression to moderate AD health state at or after the end of the full treatment schedule (i.e., 18 months) or after having amyloid clearance at month 12 will undergo the same treatment effect waning trajectories as those who complete the 18-month treatment schedule or complete due to amyloid clearance. Patients who progress to moderate AD before completing the 18-month treatment schedule (excluding those patients who met amyloid clearance criteria at month 12) will undergo the same treatment effect waning trajectories as those who discontinue due to negative stopping rules (i.e., discontinuation due to adverse events).
	Discontinuation due to AEs, including severe ARIA cases (as per SmPC)	For patients who permanently discontinue treatment due to AEs (8.86%), the model retains full treatment effect for 1 cycle (i.e., 6 months). After 6 months, treatment waning was assumed for 5 cycles (2.5 years), and 0% treatment effect was assumed at the end of the treatment waning period.
Treatment interruption	For a proportion of patients who experience non-severe ARIA, treatment is paused for a duration before re-initiation.	In the model, the RDI for donanemab was adjusted to account for a proportion of patients for whom treatment was interrupted due to non-severe ARIA cases with the duration of treatment interruption as observed from the post-hoc analysis in EU eligible patient population from TB6 trial. The RDI is intended to represent the ratio between the dose effectively administered and the target dose. An overall RDI of 97.28% was applied for donanemab, calculated as a weighted average based on the following inputs: the proportion of patients for whom treatment was interrupted due to non-severe ARIA cases (23.42%) (74), the mean duration of treatment interruption as observed from the EU eligible patient population in TB6 trial (61.9 days, or about two doses) (75), and the TB6 treatment duration (18 months or 19 x 28-day dosing cycles) (134).

The same treatment effect assumption for discontinuation due to AEs was applied to these patients.

Abbreviations: AD, Alzheimer's disease; AE, adverse event; ARIA, amyloid-related imaging abnormalities; HR, hazard ratio; IRR, infusion-related reaction; PET, positron emission tomography; RDI, Relative Dose Intensity; TB2, TRAILBLAZER-ALZ-2; TB6, TRAILBLAZER-ALZ-6

Appendix M. Additional information regarding transition probabilities

The analysis was a retrospective, observational, longitudinal cohort study using the NACC UDS (189). The objective relevant to the model was to estimate annual transition probabilities from one disease stage to a more advanced stage among a prevalent cohort of individuals with biomarker-confirmed early AD, using the Clinical Dementia Rating Scale – Sum of Boxes (CDR-SB) to define health states. There were no treatment groups. The prevalent sample was pre-specified as the primary analysis and is the sample used in the cost-effectiveness model, because transition probabilities estimated in this sample are expected to more closely resemble those observed in real-world patient populations.

The analysis used the publicly available longitudinal data from the NACC UDS, together with the NACC neuropathology (NP) data, which contains autopsy data for a subset of UDS participants (N ≈ 7,800). Key characteristics were:

- The NACC, established in 1999, maintains a cumulative database of clinical evaluations, neuropathology data (when available), and MRI imaging, contributed by more than 42 past and present Alzheimer's Disease Research Centers (ADRCs) supported by the U.S. National Institute on Aging / NIH.
- The UDS is longitudinal, with a protocol requiring approximately annual follow-up, and spans the cognitive spectrum (normal cognition, MCI, and dementia) due to a range of etiologies including AD.
- Beginning in 2015, some ADRCs began collecting select ante-mortem biomarkers, including markers of amyloid pathology (abnormally elevated amyloid on PET and abnormally low amyloid in CSF).
- This study used the commercial-use version of the NACC dataset, with data available up to the data freeze on June 1, 2023, providing information on approximately 43,000 participants contributed by 37 ADRCs.

The dataset was selected because it is a robust sample in the relevant population and, through its inclusion of MCI participants, did not need to be supplemented with literature data, reducing uncertainty. The sponsor notes that the UDS does not contain measures of medical resource use or cost, and that ante-mortem amyloid data are only available from 2015 onward.

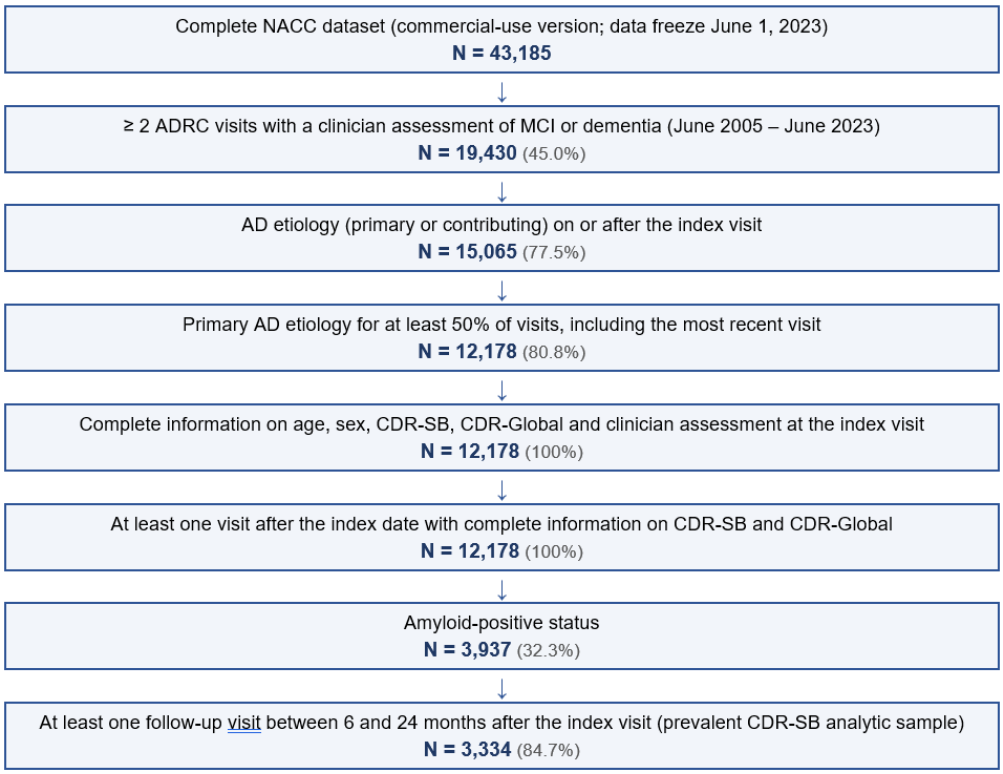
From the source population, participants were selected to capture those with cognitive impairment consistent with AD etiology who received repeat evaluation at an ADRC. The principal selection criteria were:

- ≥ 2 ADRC visits with a clinician assessment of MCI or dementia between June 2005 and June 2023 (a single such visit was retained only if an observed death occurred within one year of the index date).

- AD etiology (primary or contributing) on or after the first clinician assessment of MCI or dementia, with primary AD etiology for at least 50% of visits including the most recent visit.
- Complete demographic (age and sex) and CDR-SB and clinician assessment information at the index visit, and complete CDR-SB information at the index visit and at least the immediately following visit (or an observed death within 12 months of the index date).
- Post- or ante-mortem biomarker confirmation of amyloid positivity, defined as abnormally elevated amyloid on PET, abnormally low amyloid in CSF, frequent density of neocortical neuritic plaques, or Braak Stage V or VI for neurofibrillary degeneration on autopsy.

Applying these criteria yielded the prevalent analytic sample used in the model: n = 3,334 based on CDR-SB scores. The sequential application of these criteria is shown in Figure 23. The biomarker requirement aligns with the population eligible for amyloid-targeting therapies, which require confirmation of amyloid presence before initiation.

Figure 23 Sample selection – prevalent CDR-SB analytic sample



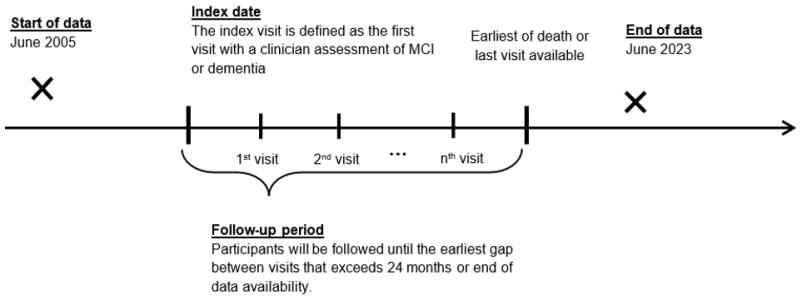
Note: Percentages denote the proportion of participants retained at each step relative to the immediately preceding step.

Baseline characteristics were assessed at the index visit. A broad set of variables was captured, including demographics (age, sex, race/ethnicity, education, living situation, marital status, region); comorbidity profile (hypertension, hypercholesterolemia,

diabetes, cardiovascular disease, cerebrovascular disease, other neurologic conditions, psychiatric disorders); number of APOE ε4 alleles; informant characteristics; cognitive characteristics (clinician evaluation, MMSE/MoCA, CDR scores); functional limitations (FAQ); and behavioral attributes (NPI-Q). Key characteristics for the prevalent (CDR-SB) sample used in the model are summarized in the table below (Table 90).

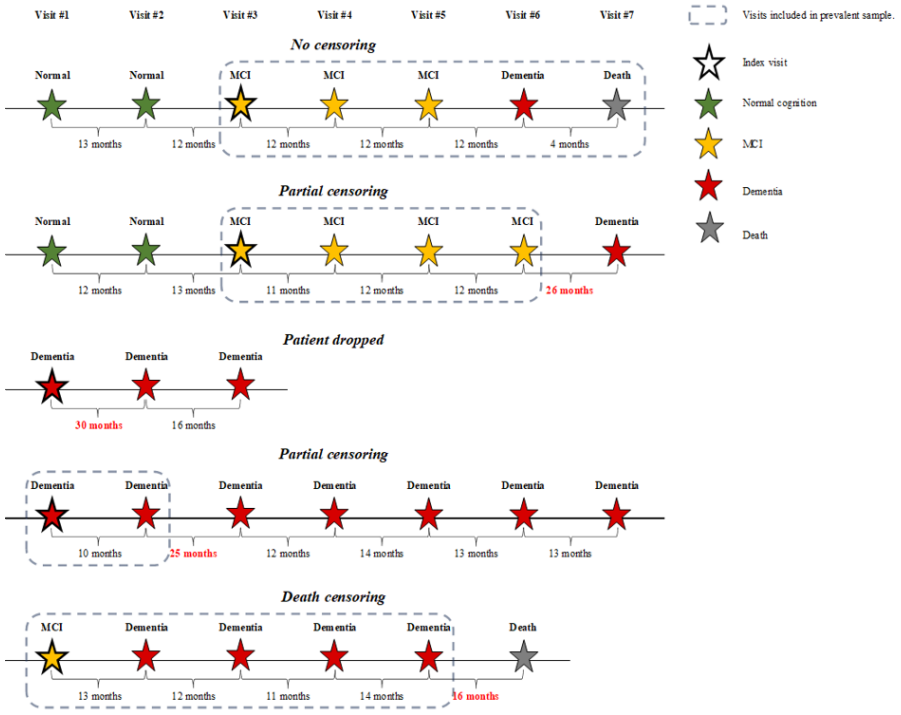
Figure 24 below outlines the NACC participant timeline.

Figure 24 NACC timelines



This study (Figure 24) estimated annual transition probabilities for NACC participants over the observable follow-up period. Only visits that are between 6 and 24 months apart were included in this analysis. Participants were censored after the first gap between visits exceeding 24 months. Death was an exception, as only deaths within 12 months of the last visit (even if the last visit was the index visit) were included in the analysis. Figure 25 below illustrates how censoring impacted included visits. Gaps exceeding 24 months between visits are indicated by bold red text. Stars represent visits, and each star is colored to reflect clinician diagnosis at that particular visit. Observations that would be included are indicated in the dashed-line box. If no dashed-line box is present, the participant would be dropped from the sample.

Figure 25 Censoring Methodology



Abbreviations: AD = Alzheimer's Disease; MCI = Mild Cognitive Impairment

Visit censoring and missing-visit imputation: While the majority of ADRC visits occurred on an annual basis, a minority of visits occurred more frequently or were significantly delayed. Participants who experienced a gap between ADRC visits < 6 months or > 24 at any point after their index visit had all visits following the unacceptable gap censored. Gaps between visits that were greater than or equal to 6 months and less than or equal to 18 months were assumed to represent a nominal annual visit. If the gap between visits was greater than 18 months but less than or equal to 24 months, it was assumed that the participant missed an annual visit. In these cases, the health state for the missing visit was imputed as follows: a) If the health state on either side of the gap was the same, the health state preceding the gap was carried forward; b) If the health state following the gap was more severe, the simple average of the CDR-SB score on either side of the gap was assigned to the missing visit. The health state of the missing visit was then assigned using the score of the outcome assessment instrument.

Non-concordance between instrument score and clinician assessment: where a validated instrument indicated normal cognition at index but the clinician assessed a more severe state, the more severe state was assigned (e.g., a clinician diagnosis of dementia with a CDR-SB score indicating normal was classified as Mild AD).

Non-monotone trajectories (no backward transitions): observed improvements in CDR-SB were treated as idiosyncratic performance or measurement variability rather than true improvement; the previous (more severe-or-equal) health state was carried

forward, so the probability of transitioning to a less severe state is zero. This is consistent with the progressive, irreversible nature of AD.

AD health states were defined using CDR-SB scores (O'Bryant et al. 2008) as shown in Table 90.

Table 90 CDR-SB health state definitions

Health state	CDR-SB score
Normal	0
Questionable / MCI	0.5 – 4
Mild AD dementia	4.5 – 9
Moderate AD dementia	9.5 – 15.5
Severe AD dementia	16 – 18

Following the approach outlined by Potashman et al (2021), multinomial logistic regression models estimated by maximum likelihood were used to estimate the annual transition probabilities from one disease state to another disease state as defined in Table 90 conditional on the initial state. This approach was used to adjust for censoring from lack of follow-up as well as simultaneous competing risks from other states. The model controlled for time between visits (in days), continuous age (in years), and sex (male, female). If death was observed within 12-months of the most recent visit, the death was assumed to have occurred exactly 365 days after the most recent visit for the purposes of the multinomial logistic model.

The multinomial model produced a transition equation for each pair of consecutive visits, which relates the predictors to the probability of transitioning to a given health state via the estimated model coefficients. The transition probability equations were then used to calculate mean transition probabilities for each pair by holding constant age, sex, and time between visits.

The probability (P_{ij}) that the first health state of a pair of visits transitions to the ith health state conditional on the health state of the initial visit j is given by:

$$\hat{P}_{ij} = \Pr(Y_j = i) = \begin{cases} \dfrac{1}{1 + \sum_{m=2}^{k} \exp(x_j \beta_m)}, if\ i = 1 \\ \dfrac{\exp(x_j \beta_m)}{1 + \sum_{m=2}^{k} \exp(x_j \beta_m)}, if\ i > 1 \end{cases}$$

where Y_j is the realized outcome, x_j is the row vector containing the fixed covariate values as well as an indicator for the initial health state j, and β_m is the coefficient vector from the model predicting transition to state m. Observed-value predictions were used to compute the predicted probabilities and 95 percent confidence intervals (95%

CIs). Because the health states are exhaustive, the sum of transition probabilities from any initial state is 1.

Standard errors and 95% CIs for the probabilities were estimated using the delta method. In the small number of cases in the alternative scenario analyses where the delta method produced unstable or non-convergent results (e.g., in situations where the transition probability function was highly non-linear in the vicinity of the expected value or the probability estimate is close to the boundaries of the probability space (0 or 1)), a bootstrap procedure – using 1,000 iterations – was used to estimate 95% CIs around the resulting transition probabilities.

The tables below (Table 91 and Table 92) present the unadjusted transition probabilities for the prevalent sample as measured by CDR-SB scores, calculated directly from the observed NACC data with no multivariable modelling. Two versions are reported: the nominal analysis (no annualization adjustment; some transitions occurred over periods longer or shorter than 365 days) and the annualized analysis (a linear annualization to a common 12-month interval). In both, rows represent the health state at the initial visit and columns the health state at the subsequent visit; probabilities in each row sum to 100%.

Table 91 Nominal unadjusted transition probabilities – prevalent sample, CDR-SB

Previous health state	Questionable / MCI	Mild AD	Moderate AD	Severe AD	Death
Questionable / MCI	70.5%	26.6%	1.4%	0.2%	1.3%
Mild AD dementia	0.0%	63.8%	30.0%	2.9%	3.3%
Moderate AD dementia	0.0%	0.0%	56.0%	30.7%	13.3%
Severe AD dementia	0.0%	0.0%	0.0%	65.7%	34.3%

Nominal unadjusted probabilities were estimated directly from the observed data with no annualization adjustment

Table 92 Annualized unadjusted transition probabilities – prevalent sample, CDR-SB

Previous health state	Questionable / MCI	Mild AD	Moderate AD	Severe AD	Death
Questionable / MCI	70.3%	26.1%	2.1%	0.2%	1.3%
Mild AD dementia	0.0%	62.3%	31.4%	3.1%	3.3%
Moderate AD dementia	0.0%	0.0%	58.0%	28.7%	13.3%
Severe AD dementia	0.0%	0.0%	0.0%	65.7%	34.3%

Annualized unadjusted probabilities were estimated directly from the observed data with a linear annualization adjustment.

AD = Alzheimer's disease; CDR-SB = Clinical Dementia Rating Scale – Sum of Boxes; MCI = mild cognitive impairment.

The probabilities applied in the cost-effectiveness model correspond to the base-case population characteristics aligned to the TRAILBLAZER-ALZ2 population, namely age 73 years, and a female proportion of 0.55 (55%). Evaluating the analysis at this exact combination reproduces the annual transition probabilities used in the model. The model uses a 6-month cycle. The probability of transitioning out of each state was

converted to an exponential rate, scaled to the cycle length, and reconverted to a probability. The probabilities for remaining in the same state (i.e., the probabilities on the principal diagonal of the trace matrix) were calculated as the difference between 100% and the row sums of scaled probabilities to ensure that the transition probabilities from each state sum to 100%. The matrix was recalculated for each comparator and at each timepoint to account for the age-varying probability of patient's death.

Comparability of the selected population from NACC, the patient population in TRAILBLAZER-ALZ2, and the relevant Danish patient population

TRAILBLAZER-ALZ2 is the appropriate source for the relative treatment effect of donanemab, as a randomised, placebo-controlled trial, but its 76-week placebo-controlled period cannot support reliable transition probabilities across the full disease spectrum: assessments were 3-monthly, the population was restricted to early symptomatic AD (MCI or mild dementia), and events in the moderate/severe states were rare. NACC, by contrast, offers a substantially larger, longitudinally followed, biomarker-confirmed cohort spanning the entire severity spectrum, making it the more appropriate source for long-term natural-history progression. Consistent with standard health-economic practice, the trial is used to establish the relative treatment effect (hazard ratio), and NACC is used to model progression under best supportive care (BSC); the two are not statistically pooled.

The two cohorts were assembled under different objectives, which explains some compositional differences between the cohorts.

- NACC prevalent CDR-SB sample (N = 3,334, Table 93): ≥2 clinician-assessed visits with MCI or dementia (June 2005–June 2023), AD etiology confirmed as the primary cause for ≥50% of visits (including the most recent), ante- or post-mortem biomarker confirmation of amyloid pathology, and complete CDR-SB/CDR-Global data. No restriction on disease severity, since state-to-state transition rates were required across the full spectrum, including moderate and severe AD.
- TRAILBLAZER-ALZ2 EU-eligible population (N = 1,218; 614 donanemab / 604 placebo, Table 94): early symptomatic AD (MMSE 20–28) in APOE ε4 non-carriers or heterozygotes, without superficial siderosis, anticoagulant use, or uncontrolled hypertension, per the EU label.

Table 93 NACC Prevalent CDR-SB Sample (N = 3,334)

Characteristic	Value
Age, years (mean ± SD)	73.3 ± 10.5
Male / Female*	50.8% / 49.2%
White	93.9%
Education, years (median)	16.0
APOE ε4: 1 copy / 2 copies / none / unknown	42.3% / 13.5% / 31.9% / 12.3%
Clinical diagnosis at index: dementia / MCI	69.8% / 30.2%
CDR-SB (mean ± SD)	5.5 ± 4.7
CDR-SB category: questionable / mild / moderate / severe	49.4% / 31.9% / 9.1% / 8.3%
MMSE (mean ± SD)	21.6 ± 7.1
FAQ (mean ± SD)	13.1 ± 9.8

Table 94 TRAILBLAZER-ALZ2 EU-Eligible Population (N = 1,218)

Characteristic	Donanemab (N=614)	Placebo (N=604)
Age, years (mean ± SD)	73.3 ± 6.3	73.5 ± 6.1
Female	61.2%	59.3%
White	90.2%	92.7%
Education ≥13 years	69.4%	72.1%
APOE ε4 heterozygous / non-carrier / homozygous	65.2% / 34.8% / 0%	65.6% / 34.4% / 0%
iADRS (mean ± SD)	104.7 ± 14.4	103.5 ± 14.5
CDR-SB (mean ± SD)	3.9 ± 2.1	4.0 ± 2.1
MMSE (mean ± SD)	22.4 ± 3.9	22.1 ± 4.0
CDR-Global = 0.5 / 1 / ≥2	60.4% / 36.1% / 3.1%	61.2% / 35.8% / 2.7%
Amyloid, Centiloids (mean ± SD)	102.6 ± 34.2	101.6 ± 33.6

Source: Jessen et al. 2026 (54)

Of the baseline characteristics presented above, age and amyloid-biomarker status are closely matched between the two populations and are not revisited here. Five characteristics show a material difference: sex composition, baseline disease-severity range, APOE ε4 genotype distribution, education, and comorbidity/psychiatric burden. Each is considered below against the natural-history progression evidence reported in the independent systematic review by Garcia et al. (2024), together with whether it was addressed in deriving the NACC transition probabilities.

The NACC prevalent sample was 49.2% female, against approximately 60% in the TRAILBLAZER-ALZ2 EU-eligible population. Garcia et al. (2024) found that female sex was not significantly associated with progression from MCI to AD dementia (HR 1.152; 95% CI 0.797, 1.665) in one study, and reported no association between sex and cognitive decline (CDR-SB or MMSE) in two further studies of MCI patients. Notwithstanding this absence of evidence for a true effect, sex was retained as a covariate in the NACC

multinomial logistic regression, and the transition probabilities shared below were recalculated at 60% female to align with the EU-eligible sex split.

NACC's prevalent sample spans the full disease continuum: 69.8% of participants already carried a clinician diagnosis of dementia at index date, with a mean CDR-SB of 5.5 and 17.4% classified as moderate or severe. TRAILBLAZER-ALZ2 EU-eligible participants were restricted by protocol to early symptomatic AD (MCI or mild dementia; MMSE 20–28), with a mean CDR-SB of approximately 4.0 and around 3% at CDR-Global ≥2 at baseline. Greater baseline cognitive impairment is among the most consistently reported prognostic factors in Garcia et al. (2024): higher CDR-SB scores were independently associated with faster subsequent progression. This difference is not addressed through a covariate; the multinomial model is estimated separately for each starting health state, so NACC's inclusion of moderate/severe participants is what allows the model to generate transition estimates that TRAILBLAZER ALZ2 alone could not produce, rather than something requiring statistical correction.

Genotype distribution differs between the populations: the NACC sample includes 13.5% ε4 homozygotes, while the TRAILBLAZER-ALZ2 EU-eligible population, being restricted to non-carriers and heterozygotes under the EU label, contains none. Restricting to evidence on natural disease progression, Garcia et al. (2024) reported mixed findings: one study found APOE4 carriage was not significantly associated with progression from MCI to AD dementia over 1.47 years, while a second found that one copy of the APOE4 allele increased the risk of fast progression on the CDR-SB scale over a mean of 3.6 years relative to non-carriers (OR 1.94; 95% CI 1.08, 3.47), but that two copies (homozygosity) did not increase the risk of either fast or slow progression. Given this mixed evidence, and the absence of a demonstrated effect for homozygosity specifically, this imbalance is not expected to have an impact on the natural disease progression.

Median education was 16 years in the NACC sample, compared with approximately 70% of the TB2 EU-eligible population having completed at least 13 years; both reflect comparatively well-educated populations, and the two metrics are not directly equivalent. Garcia et al. (2024) reviewed education in two studies and found no clear relationship with disease progression, therefore no impact is expected.

In summary, sex is adjusted for despite the absence of a demonstrated effect, and baseline severity is addressed through the model's state-conditional structure; APOE genotype and education remain unadjusted, reflecting mixed, absent, or unextracted evidence of a natural-progression effect in the reviewed literature (Garcia et al 2024).

A multinomial logistic regression (maximum likelihood) was fitted to NACC visit-pairs from the same CDR-SB prevalent sample described in further detail in the response to the question above, controlling for continuous age, sex, and time between visits.

Two covariate scenarios were run using the accompanying look-up tool: (i) a scenario approximating the overall TB2 trial population (age 73, 55% female), and (ii) an EU-eligible scenario (age 73, 60% female, matching the observed TRAILBLAZER-ALZ2 EU-eligible sex split). The resulting matrices are materially similar, differing by no more than 0.5 percentage points, concentrated in the moderate- and severe-AD rows:

Table 95 Annual adjusted transition probabilities (original and EU eligible patient population)

	Next Health State				
Previous Health State	**Questionable/MCI**	**Mild AD Dementia**	**Moderate AD Dementia**	**Severe AD Dementia**	**Death**
Adjusted for baseline age (73 years and 55% female) – overall TRAILBLAZER-ALZ population					
Questionable/MCI	71.1% (69.7%, 72.6%)	26.4% (24.9%, 27.8%)	1.4% (1.0%, 1.7%)	0.2% (0.1%, 0.2%)	1.0% (0.7%, 1.2%)
Mild AD Dementia	0.0% (0.0%, 0.0%)	64.8% (63.2%, 66,4%)	29.7% (28.2%, 31.2%)	2.9% (2.3%, 3.4%)	2.6% (2.1%, 3.1%)
Moderate AD Dementia	0.0% (0.0%, 0.0%)	0.0% (0.0%, 0.0%)	57.4% (55.1%, 59.7%)	32.3% (30.2%, 34.5%)	10.3% (8.9%, 11.6%)
Severe AD Dementia	0.0% (0.0%, 0.0%)	0.0% (0.0%, 0.0%)	0.0% (0.0%, 0.0%)	70.7% (68.5%, 72.9%)	29.3% (27.1%, 31.5%)
Adjusted for baseline age (73 years and 60% female) – EU eligible population					
Questionable/MCI	71.0 (69.6%, 72.5%	26.5% (25.0%, 27.9%)	1.4% (1.0%, 1.7%)	0.2% (0.1%, 0.2%)	1.0% (0.7%, 1.2%)
Mild AD Dementia	0.0% (0.0%, 0.0%)	64.8% (63.2%, 66.4%)	29.8% (28.2%, 31.3%)	2.9% (2.3%, 3.4%)	2.6% (2.1%, 3.0%)
Moderate AD Dementia	0.0% (0.0%, 0.0%)	0.0% (0.0%, 0.0%)	57.5% (55.1%, 59.8%)	32.4% (30.2%, 34.6%)	10.1% (8.7%, 11.4%)
Severe AD Dementia	0.0% (0.0%, 0.0%)	0.0% (0.0%, 0.0%)	0.0% (0.0%, 0.0%)	71.2% (69.0%, 73.4%)	28.8% (26.6%, 31.0%)

Overall, the NACC dataset was chosen because it is a robust sample in the relevant population for the decision problem, and its inclusion of MCI patients means it did not need to be supplemented with additional data from the literature, thereby reducing uncertainty in the model.

Improvement in condition observed in NACC

In the NACC observational analysis used to estimate the natural-history transition probabilities, some participants were observed to move to a less severe health state between visits — i.e., an apparent improvement in CDR-SB score over time.

These observed improvements were not treated as true clinical improvement. Alzheimer's disease is a progressive, irreversible condition, so an observed reduction in impairment over time is considered to reflect idiosyncratic day-to-day performance or measurement variability in the assessment instrument rather than a genuine reversal of the underlying disease. This was therefore handled by an explicit adjustment before the transition probabilities were estimated, as follows. Where a participant was observed to improve to a less severe health state, the improved state was reassigned by carrying forward the preceding (more severe-or-equal) health state, on the assumption that the visit represented a continuation of the prior state. The same principle was applied in the missing-visit imputation: where the health states bracketing a visit gap were the same, the preceding state was carried forward.

As a direct consequence, the estimated (adjusted) transition matrix contains no backward transitions — the probability of moving to a less severe state is 0%. The estimated effect therefore reflects only stability or progression, consistent with the clinical course of AD. This is a deliberate refinement over earlier NACC-based analyses (e.g., Potashman et al. 2021), which permitted improvement transitions that are inconsistent with the progressive nature of the disease.

Comparison of patient movements in the TRAILBLAZER-ALZ2 and NACC

The patient movements in TRAILBLAZER-ALZ2 can be seen in the Sankey diagram in an earlier question. In the NACC analysis, all patients who met the inclusion criteria were

considered for the analysis, therefore the starting population is not restricted to patients who have MCI or mild AD as it was in TRAILBLAZER-ALZ2. In addition, we don't have the data available by different timepoints as displayed in the Sankey diagram; only the nominal or annualized (non-adjusted) transition probabilities as observed in NACC available (see also response above) NACC is a real-world observational study in which the assessment visits are pre-dominantly conducted on an annual basis hence the nominal and non-adjusted annualized data are very similar.

Additional data sources explored but not used

Different sources that could be used to inform transition probabilities in the model were explored. For instance, Wimo et al. 2020 provided transition probabilities based on a Swedish dementia registry starting from 2007. The natural progression rates were estimated based on 53,880 persons with AD dementia staged per MMSE (mild: 21–30, moderate: 10–20, severe 0–9). Because the analysis grouped MMSE 21–30 together, there was no transition probability specific to MCI due to AD. Vos et al. 2015 reported a three-year progression risk of 50% per the International Working Group-1 (IWG-1) diagnostic criteria based on their review of 1,607 patients with MCI in multiple centres. Therefore, assuming a constant hazard, an annual transition rate can be derived from MCI due to AD to mild AD dementia (20.6%), which can be applied assuming no transition to other AD dementia stages. The AD dementia patients included in the analysis of the Swedish dementia registry database did not have amyloid beta status confirmed and therefore are not in line with the population assessed in the decision-problem.

The EU-GERAS study, a prospective observational study conducted in the UK, Germany and France was also explored for transition probabilities. However, patients didn't require amyloid confirmation to participate in this study and patients with MCI due to AD dementia were not enrolled into this study, which requires the transition probabilities to be supplemented by the literature and therefore additional assumptions. None of the studies included the CDR, hence no transition probabilities could be estimated increasing uncertainty in the model due to the inconsistencies in the scales for key parameters.

Transition probabilities based on TRAILBLAZER-ALZ 2 were also explored. Within the trial, clinical outcome assessments were conducted every 3 months. For the calculation of transition probabilities, similar results indicating the same disease health state at two consecutive visits were required to ensure stability in estimating progression and reduce potential scale noise in line with the approach applied in the NACC analysis. Given the 18-month timeframe of the trial, the data collected are therefore not sensitive enough to accurately inform the transition probabilities. Additionally, as the trial population was primarily made up of patients with MCI due to AD and mild AD dementia, reliable information on the risk of transitioning into more severe health states is not available from the trial.

Therefore, due to the trial design and relatively short timeframe (18 months) of the TRAILBLAZER-ALZ 2 trial, it was not possible to collect reliable long-term data on transition probabilities within the trial.

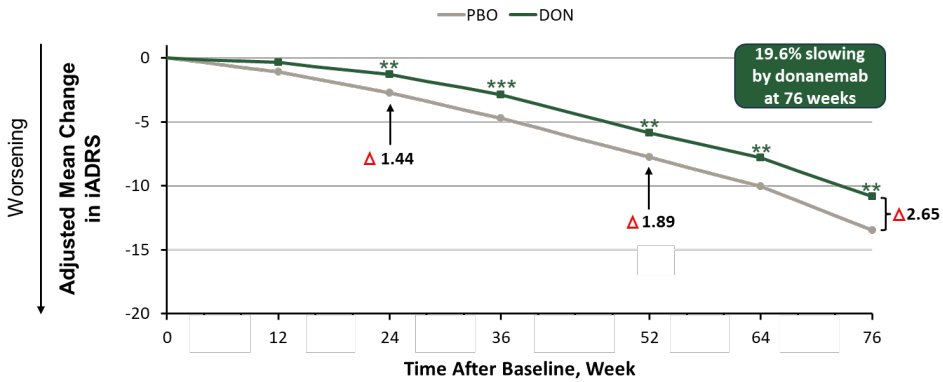
Appendix N. Overview of statistical approaches employed in TRAILBLAZER-ALZ2

Table 96 Overview of statistical approaches in TRAILBLAZER-ALZ2

Statistical test	Endpoints analysed	Notes
NCS2	All clinical outcomes (except CDR-SB)	▪ Dependent variable: baseline score and each scheduled post-baseline score ▪ Fixed effects: NCS basis expansion terms (2 terms), NCS basis expansion term x treatment interaction (2 terms), baseline age, concomitant AChE inhibitors and/or memantine use at baseline (yes/no), randomized stratifying factors (pooled site and baseline tau category [baseline tau category in overall population only])
MMRM	CDR-SB	▪ Dependent variable: change from baseline ▪ Fixed effects: age, baseline value, visit as a categorical variable, treatment, baseline x visit interactions, treatment x visit interactions, concomitant AChE inhibitors/memantine use at baseline (CDR-SB only), randomization stratifying factors (pooled site and baseline tau category [overall population only])
Time-PMRM	iADRS and CDR-SB (slowing in time to disease progression)	▪ Used to estimate slowing of time to disease progression due to donanemab vs placebo group ▪ Dependent variables: baseline and post-baseline endpoint measurements at scheduled visits ▪ Fixed effects: baseline age, concomitant AChE inhibitors/memantine use at baseline (yes/no), pooled investigator, baseline tau category (overall population only)
Cox proportional hazards models	CDR-G, iADRS (MWPC), CDR-SB (MWPC)	▪ Analysis modelled as time to first occurrence of the event: – Any increase in CDR-G from baseline. – ≥1 point increase in CDR-SB from baseline for MCI or ≥2 point increase from baseline for mild AD – ≥5 point decrease in iADRS from baseline for MCI or ≥9 point decrease from baseline for mild AD ▪ Adjusted for baseline age, score, concomitant AChE inhibitor/memantine at baseline (yes/no)
GLMM	CDR-SB (non-progression)	▪ Non-progression (CDR-SB change from baseline ≤0) calculated as a binary outcome at each scheduled visit ▪ Dependent variable: non-progressing status (yes/no) ▪ Fixed effects: baseline score, baseline score-by-visit interaction, treatment, visit, treatment-by-visit interaction, concomitant AChEI and/or memantine use at baseline (yes/no), age at baseline, baseline tau category (overall population only)

Appendix O. Figures for outcome measures from TRAILBLAZER-ALZ2 including its long-term extension

Figure 26 Change from baseline to Week 76 in iADRS in the EU SmPC population* of TRAILBLAZER-ALZ2, conservative J2R/CIR analysis^ (MMRM)



PBO, n	730	730	730	730	730	730	730
DON, n	717	717	717	717	717	717	717

**p<0.01; ***p<0.001 vs placebo.

* Overall EU SmPC population includes all randomised participants in TRAILBLAZER-ALZ2 excluding APOE ε4 homozygotes.

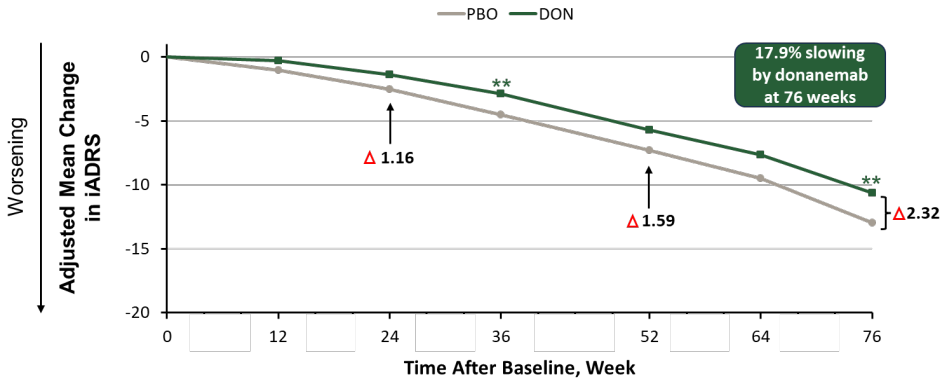
^ Conservative analytical method: Missing values were multiple imputed with J2R method when data was missing for participants with discontinuation due to death or severe, symptomatic, or serious ARIA events, and CIR was used when data was missing for other reasons.

CI 95%: Week 24 = (0.55, 2.33); Week 52 = (0.65, 3.13); Week 76 = (1.04, 4.26)

Abbreviations: CIR, copy increment reference method; DON, donanemab; iADRS, integrated Alzheimer's Disease Rating Scale; J2R, jump to reference method; MMRM, mixed models for repeated measures; PBO, placebo.

Source: EPAR, Kisunla, INN-donanemab

Figure 27 Change from baseline to Week 76 in iADRS in the EU eligible population* of TRAILBLAZER-ALZ2, conservative J2R/CIR analysis^ (MMRM)



PBO, n	601	601	601	601	601	601	601
DON, n	612	612	612	612	612	612	612

**p<0.01.

* Overall EU eligible population includes all randomised participants in TRAILBLAZER-ALZ2 excluding APOE ε4 homozygotes, patients with baseline superficial siderosis, anticoagulant use and poorly controlled blood pressure (systolic blood pressure ≥ 140 and diastolic blood pressure ≥ 90).

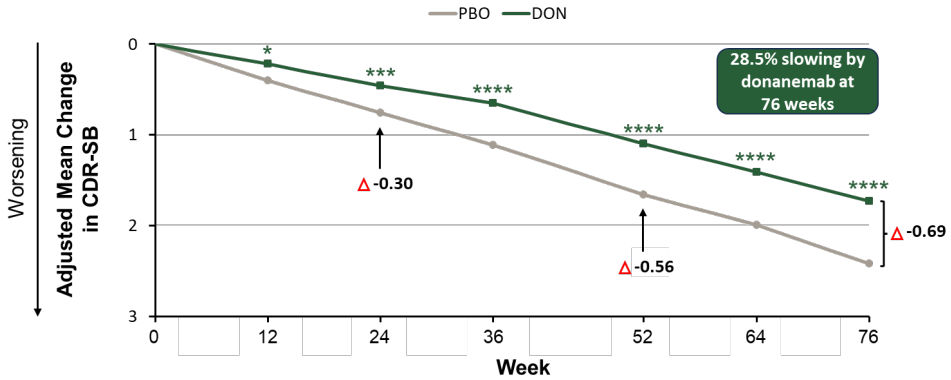
^ Conservative analytical method: Missing values were multiple imputed with J2R method when data was missing for participants with discontinuation due to death or severe, symptomatic, or serious ARIA events, and CIR was used when data was missing for other reasons.

CI 95%: Week 24 = (0.23,2.09); Week 52 = (0.35, 2.82); Week 76 = (0.69, 3.95)

Abbreviations: CIR, copy increment reference method; DON, donanemab; iADRS, integrated Alzheimer's Disease Rating Scale; J2R, jump to reference method; MMRM, mixed models for repeated measures; PBO, placebo.

Source: Jessen 2026 (54)

Figure 28 Change from baseline to Week 76 in CDR-SB in the EU SmPC population[a] of TRAILBLAZER-ALZ2, conservative J2R/CIR analysis[b] (MMRM)



PBO, n	730	730	730	730	730	730	730
DON, n	717	717	717	717	717	717	717

*p<0.05; **p<0.01, ***p<0.001, ****p<0.0001 vs placebo.

[a] Overall EU SmPC population includes all randomised participants in TRAILBLAZER-ALZ2 excluding APOE ε4 homozygotes.

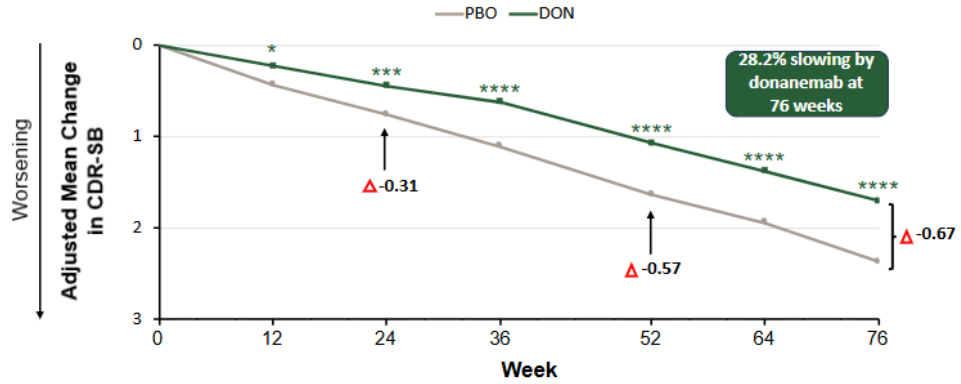
[b] Conservative analytical method: Missing values were multiple imputed with J2R method when data was missing for participants with discontinuation due to death or severe, symptomatic, or serious ARIA events, and CIR was used when data was missing for other reasons.

CI 95%: Week 24 = (-0.45, -0.15); Week 52 = (-0.77, –0.35); Week 76 = (-0.95, -0.43)

Abbreviations: CDR-SB, Clinical Dementia Rating Scale – Sum of Boxes; CIR, copy increment reference method; DON, donanemab; J2R, jump to reference method; MMRM, mixed models for repeated measures; PBO, placebo.

Source: EPAR, Kisunla, INN-donanemab

Figure 29 Change from baseline to Week 76 in CDR-SB in the EU eligible population* of TRAILBLAZER-ALZ2, conservative J2R/CIR analysis^ (MMRM)



PBO, n	601	601	601	601	601	601	601
DON, n	612	612	612	612	612	612	612

*p<0.05; **p<0.01, ***p<0.001, ****p<0.0001 vs placebo.

[*] Overall EU eligible population includes all randomised participants in TRAILBLAZER-ALZ2 excluding APOE ε4 homozygotes, patients with baseline superficial siderosis, anticoagulant use and poorly controlled blood pressure (systolic blood pressure ≥ 140 and diastolic blood pressure ≥ 90).

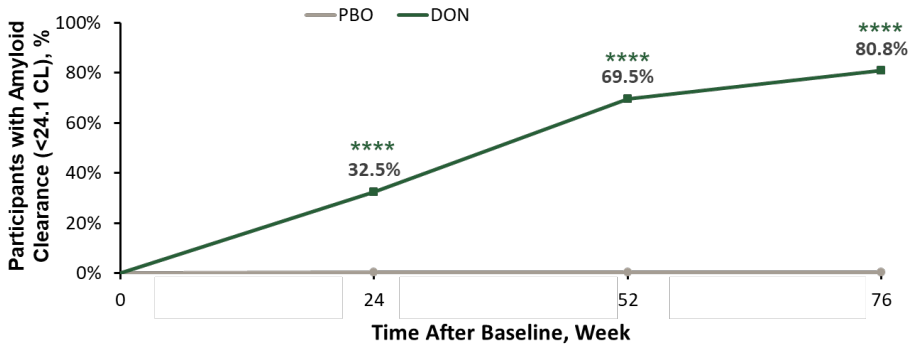
[^] Conservative analytical method: Missing values were multiple imputed with J2R method when data was missing for participants with discontinuation due to death or severe, symptomatic, or serious ARIA events, and CIR was used when data was missing for other reasons.

CI 95%: Week 24 = (-0.48, -0.15); Week 52 = (-0.81, -0.33xx); Week 76 = (-0.97, -0.37)

Abbreviations: CDR-SB, Clinical Dementia Rating Scale – Sum of Boxes; CIR, copy increment reference method; DON, donanemab; J2R, jump to reference method; MMRM, mixed models for repeated measures; PBO, placebo.

Source: Jessen 2026 (54)

Figure 30 Proportion of participants achieving amyloid clearance[a] at Weeks 24, 52, and 76 of TRAILBLAZER-ALZ2 in EU SmPC population[b,c,d,e]



PBO, n	664	603	564
DON, n	633	561	515

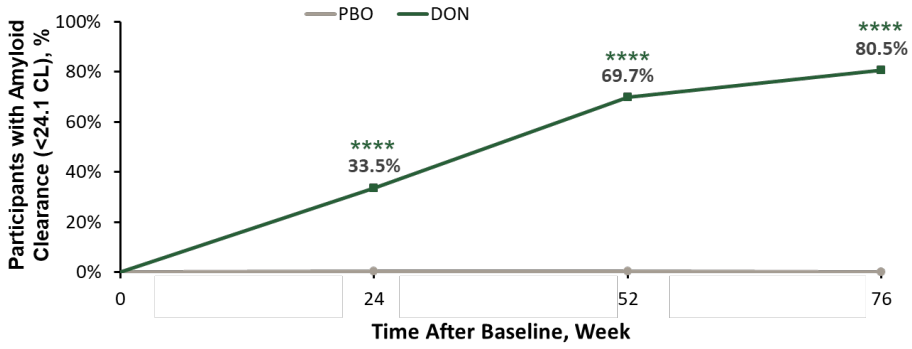
[a] Amyloid plaque clearance defined as a level of <24.1 CL, which equates to a negative visual read on an amyloid PET scan.

[b] Placebo across all endpoints ranged from 0.0-0.2%
[c] Statistical method: Fisher's exact test
[d] Analysis method: Prespecified
[e] EU SmPC population includes all randomised participants in TRAILBLAZER-ALZ2 excluding APOE ε4 homozygotes.

For CI 95% see Table 18

Abbreviations: CL, centiloid; DON, donanemab; PBO, placebo.
Source: Lilly Data on File.

Figure 31 Proportion of participants achieving amyloid clearance[a] at Weeks 24, 52, and 76 of TRAILBLAZER-ALZ2 in EU eligible population[b,c,d,e]



PBO, n	547	492	464
DON, n	547	491	451

****p<0.0001 vs placebo

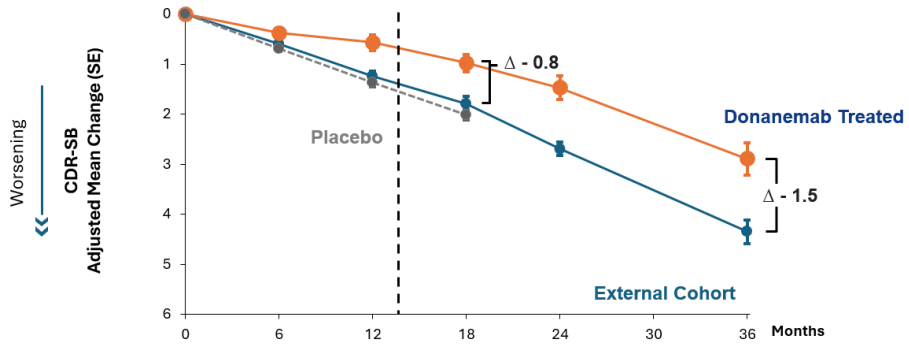
[a]Amyloid clearance defined as <24.1 CL (Navitsky et al, 2018) on amyloid PET and is consistent with sparse to no neuritic plaques and a visually negative read of the PET scan.
[c]Analysis method: Fisher's exact test
[d] Analysis method: Prespecified, Post-hoc population
[e] Placebo across all endpoints ranged from 0.0-0.2%

For CI 95% see Table 18

Abbreviations: CL, centiloid; DON, donanemab; PBO, placebo.

Source: Jessen 2026 (54)

Figure 32 Change from baseline to month 36 in CDR-SB in participants who completed treatment at month 12 (EU SmPC population)



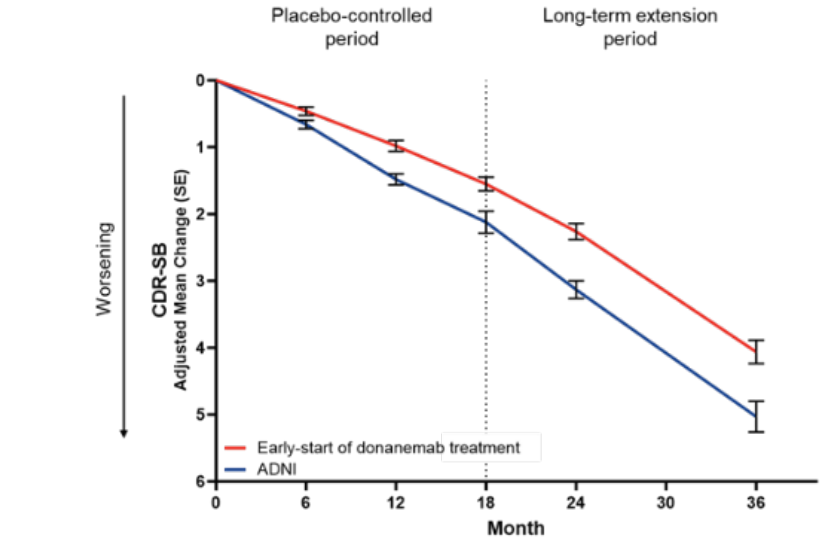
Donanemab	171	166	166	159	140	112
External Cohort (ADNI)	210	198	183	153	141	95
Placebo	694	643	584	556		

CI 95%: Month 18 = (-1.26, -0.38); Month 36 = (-2.23, –0.69)

Abbreviations: ADNI, Alzheimer's Disease Neuroimaging Initiative; CDR-SB, Clinical Dementia Rating-Sum of Boxes; LTE, Long-term Extension; PBO, Placebo; SE=Standard Error

Source: Lilly Data on File.

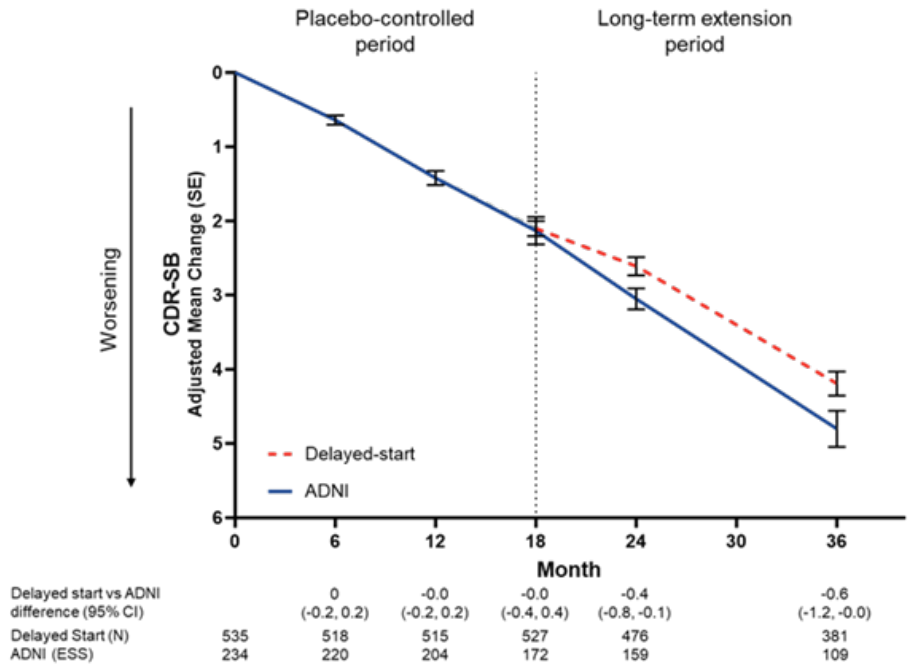
Figure 33 Clinical efficacy measured by change from baseline in the CDR-SB score - early start analysis (EU SmPC population)



Early-start vs ADNI difference (95% CI)		-0.2 (-0.4, -0.1)	-0.5 (-0.7, -0.3)	-0.6 (-0.9, -0.2)	-0.9 (-1.2, -0.5)	-1.0 (-1.5, -0.4)
Early-start (N)	661	610	547	506	428	352
ADNI (ESS)	210	198	183	153	141	95

Abbreviations: ADNI, Alzheimer's Disease Neuroimaging Initiative; CDR-SB, clinical dementia rating – sum of boxes; ESS, effective sample size: PC, placebo controlled; SE, standard error.
ADNI cohort was weighted using propensity score using average treatment effect on the treated weights; CDR-SB change from baseline were estimated with MMRM model using ADNI weights. Dashed line indicates 18-month timepoint. Double-blind period occurred 0-18 months; long-term extension period 18-36 months.
Source: Jessen et al, 2026, supplement (54)

Figure 34 Clinical efficacy measured by change from baseline in the CDR-SB score - delayed start analysis (EU SmPC population)

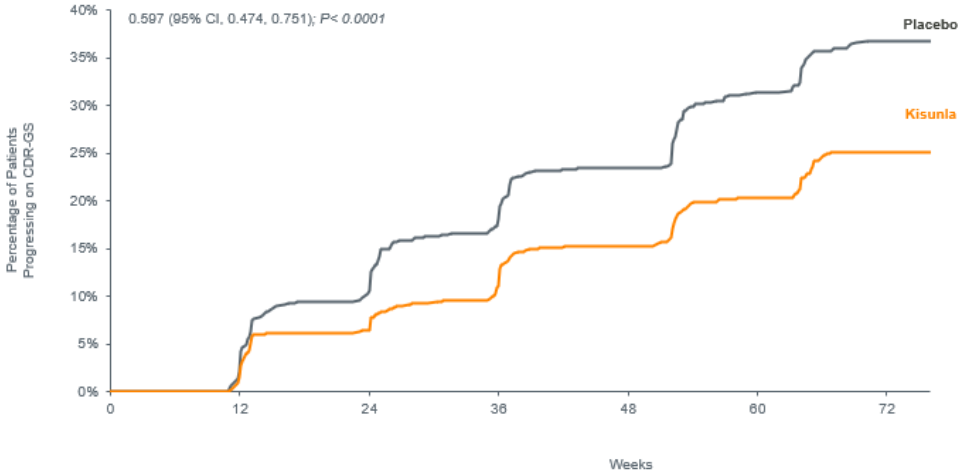


Abbreviations: ADNI, Alzheimer's Disease Neuroimaging Initiative; CDR-SB, clinical dementia rating – sum of boxes; ESS, effective sample size: PC, placebo controlled; SE, standard error.

ADNI cohort was weighted using propensity score using average treatment effect on the treated weights; CDR-SB change from baseline were estimated with MMRM model using ADNI weights. Dashed line indicates 18-month timepoint. Double-blind period occurred 0-18 months; long-term extension period 18-36 months.

Source: Jessen et al, 2026, supplement (54)

Figure 35 EU SmPC population CDR-G risk of progression to a later clinical stage (Baseline to Week 76)



Prespecified endpoint: Cox regression model; ARIA and deaths counted as progression.

AD=Alzheimer's Disease; APOE ε4, Apolipoprotein E type ε4 Allele; CDR-GS, Clinical Dementia Rating–Global Scale; CDR-SB, Clinical Dementia Rating-Sum of Boxes; CIR, Copy Increment in Reference; HR=Hazard Ratio; J2R=Jump to Reference; MMRM=Mixed Model Repeated Measures; P=Probability value.

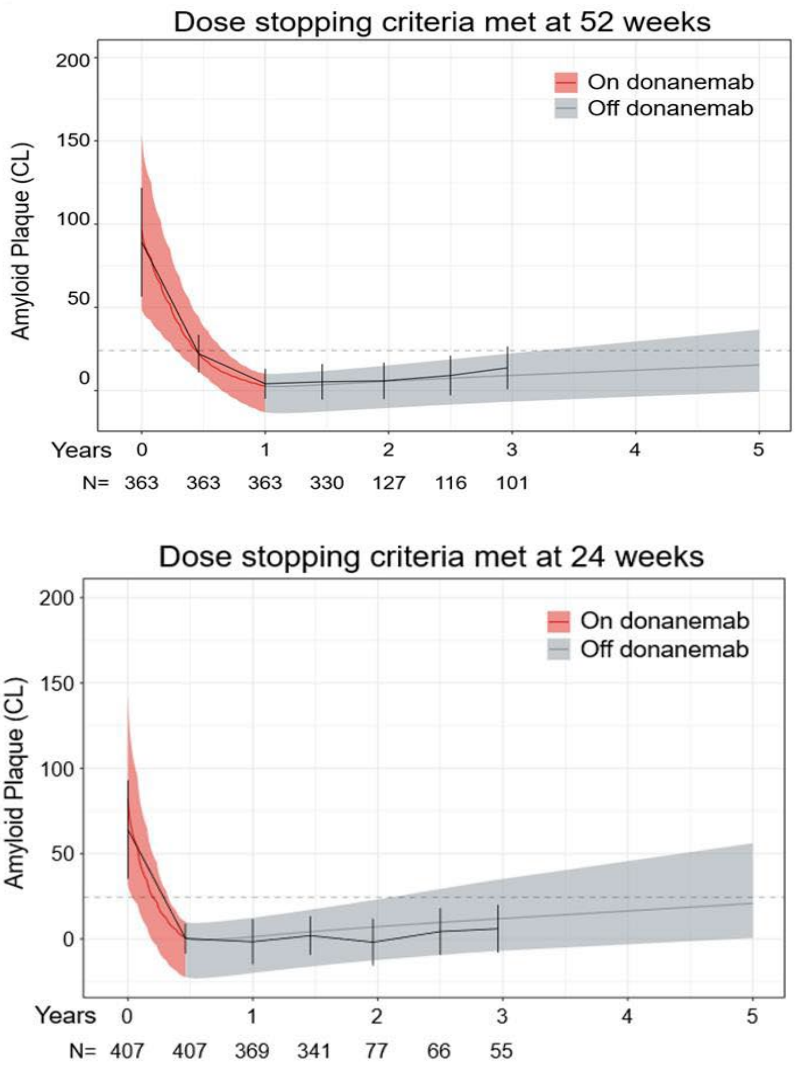
Source: Eli Lilly, Data on File.

Figure 36 TRAILBLAZER-ALZ2; Placebo versus Weighted ADNI Cohort up to 18 Months (EU SmPC population)



Abbreviations: ADNI = Alzheimer's Disease Neuroimaging Initiative; CDR-SB, Clinical Dementia Rating – Sum of Boxes; Dona, donanemab; ESS, effective sample size; LTE, long-term extension; MMRM, mixed model of repeated measures; TB2, TRAILBLAZER-ALZ2
Source: Lilly Data on file.

Figure 37. Amyloid plaque re-accumulation on florbetapir F 18 PET in participants who completed donanemab treatment at 24 weeks and 52 weeks, modelled using data from across studies AACD, TRAILBLAZER-ALZ, TRAILBLAZER-EXT, and TRAILBLAZER-ALZ2 PC & LTE



CL = Centiloids; LTE, long-term extension; N, number of participants; PC, placebo-controlled; SD, standard deviation. Participants completing active donanemab treatment at 24 weeks or 52 weeks. Shaded region indicates 90% prediction interval, solid line is predicted median, red region depicting participants on treatment (to Week 24 or 52) and then off-treatment (grey region). Observed data (median, SD) is shown by black solid bars. Dotted line indicates <24.1 CL.

Left panel: Simulated amyloid plaque level over time using exposure response model and stratified by participants achieving <11 CL by 24 weeks and then discontinuing donanemab treatment.

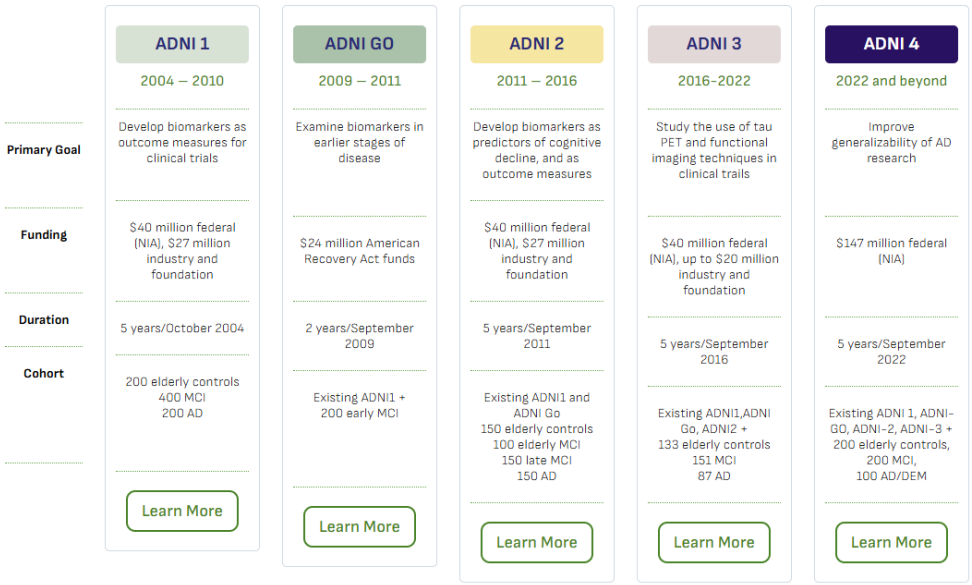
Right panel: Simulated amyloid plaque level over time using exposure-response model and stratified by participants achieving amyloid plaque <11 centiloids at Week 52 or between 11 and <25 at 24 and 52 weeks and then discontinuing donanemab treatment.

Source: Lilly data on file.

Appendix P. ADNI database and methodology used in the comparison of progression in TB2

The ADNI database (Figure 38) was used as it provides key information on AD biomarker positivity and the relevant outcome of CDR-SB. The ADNI study began in 2004 and is a longitudinal, multicenter, observational study with data on over 2,400 participants with AD. ADNI data are publicly available to researchers around the world with an overall goal to validate biomarkers for AD clinical trials (190). Participants in this data set represent an amyloid-targeting therapy-naïve AD population that, when matched to TRAILBLAZER-ALZ2, can be used as a basis for comparison.

Figure 38 Description of ADNI dataset



Note: We relied on a dataset with patients from ADNI1, ADNI GO, ADNI2, and ADNI3, but due to our selection criteria (cut off on baseline CSF total tau/abeta 42 ratio using Roche Elecsys assay), we only included patients recruited under ADNI1 (n = 216), ADNIGO (n = 42), and ADNI2 (n = 281). Excluding APOE4 homozygous will change the number of patients from the various datasets.

For both data sources, patient-level longitudinal data were used. The treatment effect analysis was performed on the APOE4 non-homozygote (ie. APOE 4 heterozygote and APOE4 non-carrier) population of the TRAILBLAZER-ALZ2 LTE trial and the non-homozygote population of the ADNI cohort.

To replicate the key TRAILBLAZER-ALZ2 inclusion criteria, ADNI patients were selected if they were cognitively impaired, non-homozygote and were amyloid positive (assessed by having a CSF total-tau/Aβ42 ratio >0.28, (191)). The National Institute on Aging and the

Alzheimer's Association (NIA-AA) revised criteria for diagnosis and staging of Alzheimer's disease classifies CSF hybrid ratios, including total-tau/Aβ42 as a core 1 biomarker that is highly concordant with amyloid positivity on PET (192).

To ensure the balance in patient and disease characteristics of the placebo arm of the TRAILBLAZER-ALZ2 trial and the selected ADNI population, a propensity score (PS) weighting method was performed. PS weights were calculated for the ADNI selected cohort with the ATT (average treatment effect on the treated) estimand using the inverse probability weighting method (calculated with the generalized linear model (GLM) method using the WeightIt package in R (version 4.4.2)) (193-195). The following baseline covariates were included in the weighting procedure: age, sex, APOE4 non-carrier status and heterozygote status, Clinical Dementia Rating Scale – Sum of Boxes (CDR-SB) score at baseline, Alzheimer's Disease Assessment Scale-Cognitive Subscale 13 (ADAS-Cog13) at baseline and Mini-Mental Score Evaluation (MMSE) score (at baseline for ADNI and at screening for TRAILBLAZER-ALZ2 given the TRAILBLAZER-ALZ2 criterion on MMSE was applied at screening in the trial). Information on AChEI/memantine use was not routinely collected and is not available in the ADNI dataset. It was therefore not possible to include this as a matching criterion. All common variables between the two datasets were adjusted for, apart from amyloid Centiloids levels due to high levels of missing data in the ADNI selected cohort. Data on anticoagulant use, poorly controlled hypertension and superficial siderosis are not routinely collected in ADNI, therefore it was not possible to focus on the EU eligible patient population in the analysis.

Propensity weights were checked to ensure balanced covariates (standardized mean difference <0.1 for each covariate) and to assess the presence of extreme weights (trimmed to the 95th percentile for a weight higher than the 95th percentile) and impact on the effective sample size (196).

Finally, two mixed model for repeated measures (MMRM) models were run on the CDR-SB change from baseline: a first model using TRAILBLAZER-ALZ2 placebo arm data and weighted ADNI cohort up to month 18 to check that the progression of decline of the weighted ADNI was similar to the decline observed in the TRAILBLAZER-ALZ2 placebo arm, and a second model to get estimate a treatment effect estimate at month 36 using TRAILBLAZER-ALZ2 donanemab and the weighted ADNI cohort. The MMRM model used was similar to the planned MMRM model for CDR-SB change from baseline in the TRAILBLAZER-ALZ2 statistical analyses plan with visits at month 6, 18, 24 and 36. The model covariates were: treatment, age, APOE E4 non-carrier and heterozygote status, baseline CDR-SB, baseline ADAS-Cog13, study entry MMSE, visit, and the interactions visit*treatment and visit*baseline CDR-SB.

Sensitivity analyses were run to ensure the robustness of the base case, including modifications in the weighting method, the chosen population, and the covariate choice.

Three different weighting methods were used to estimate the weights: the GLM method, from our base-case analysis, the GBM (Generalized Boost Model) and the entropy balancing methods. Those three methods differ in the way of estimating weights and balancing covariates. GLM is widely accepted and is optimal for well specified covariates. GBM, a more complex machine learning method, uses boosted regression trees to

capture unknown or more complex covariate-treatment relationships. Entropy balancing focuses on achieving perfect covariate balance.

In addition, three subpopulations were considered by selecting patients who switched from donanemab to placebo due to meeting dosing cessation criteria at month 6 or 12, at month 12 or at month 6 or 12 or 18. Donanemab-treated participants could switch to placebo in a blinded manner during TRAILBLAZER-ALZ2 if they met either: 1) amyloid level was <11 CL at any single amyloid PET scan, or 2) amyloid level was ≥11 to <25 CL in two consecutive amyloid PET scans.

This analysis provides evidence of donanemab-treated patients after stopping the treatment to address the uncertainty of the long-term treatment effect beyond discontinuation.

Results

Of the 2,430 participants in the ADNI cohort (from the cutoff date of January 10th, 2025 for ADNIMERGE data set), 1,535 were cognitively impaired and of those, 539 patients were amyloid positive according to the CSF total-tau/Aβ42 ratio and 427 patients were APOE4 non-homozygote[11]. Out of those, 422 had non-missing covariates[12]. These 422 patients were weighted in line with the baseline characteristics of the placebo arm of the TRAILBLAZER-ALZ2 trial. The effective sample size after weighting (that can be interpreted as the number of patients contributing to the analysis based on the size of the weights) of the ADNI cohort was 210[13].

Based on the propensity weight diagnosis, demographic and baseline characteristics were well balanced between TRAILBLAZER-ALZ2 placebo and the weighted ADNI cohort (Table 97 and Figure 39) and the weights before and after trimming displayed in (Figure 40) show limited high weights before trimming.

Table 97. Demographic and Baseline Characteristics of the EU SmPC population before and after Weighting (Following Trimming)

Baseline characteristics	TB2 EU SmPC population Placebo (N=702)	ADNI Before Weighting (N=422)	ADNI After Weighting (ESS=210)
Age, mean (SD)	73.64 (6.08)	74.71 (7.35)	73.56 (8.27)
Gender, male (%)	293 (41.7)	246 (58.3)	314.7 (45.5)
APOE4 Non-Carrier (%)	240 (34.2)	154 (36.5)	228.3 (33.0)
MMSE, mean (SD)	23.64 (2.49)	25.83 (2.78)	23.58 (2.69)

[11] Reference: Eli Lilly, Data on file, 2025a

[12] Reference: Eli Lilly, Data on file, 2025b

[13] Reference: Eli Lilly, Data on file, 2025b

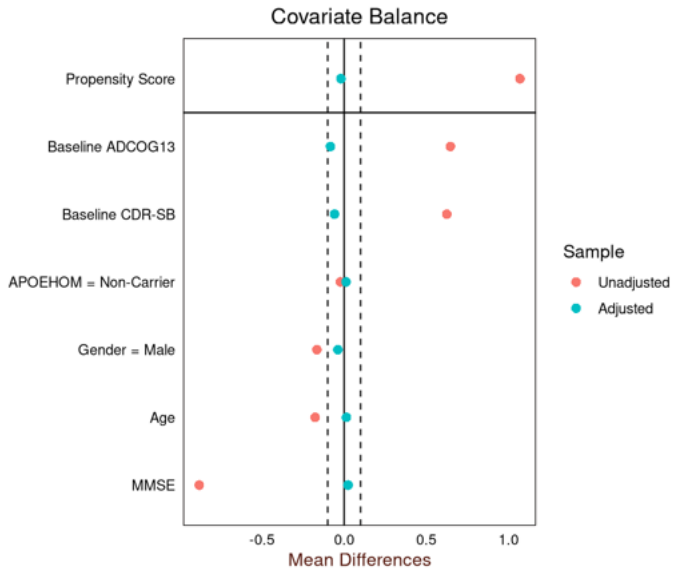
Baseline characteristics	TB2 EU SmPC population Placebo (N=702)	ADNI Before Weighting (N=422)	ADNI After Weighting (ESS=210)
ADAS-Cog13, mean (SD)	28.97 (8.85)	23.25 (9.35)	29.70 (9.87)
CDR-SB, mean (SD)	3.96 (2.06)	2.67 (1.79)	4.08 (2.03)

Note: Key variables to derive the EU eligible patient population was not sufficiently captured in the ADNI cohort, hence the analysis focused on the EU SmPC population.

Abbreviations: ADAS-Cog13, 13-Item Alzheimer's Disease Assessment Scale – Cognitive Subscale; ADNI, Alzheimer's Disease Neuroimaging Initiative; APOE4, apolipoprotein E ε4 (non-carrier vs heterozygote); CDR-SB, Clinical Dementia Rating – Sum of Boxes; Dona, donanemab; ESS, effective sample size; LTE, long-term extension; MMSE, Mini-Mental State Exam

Source: Eli Lilly, Data on file, 2025

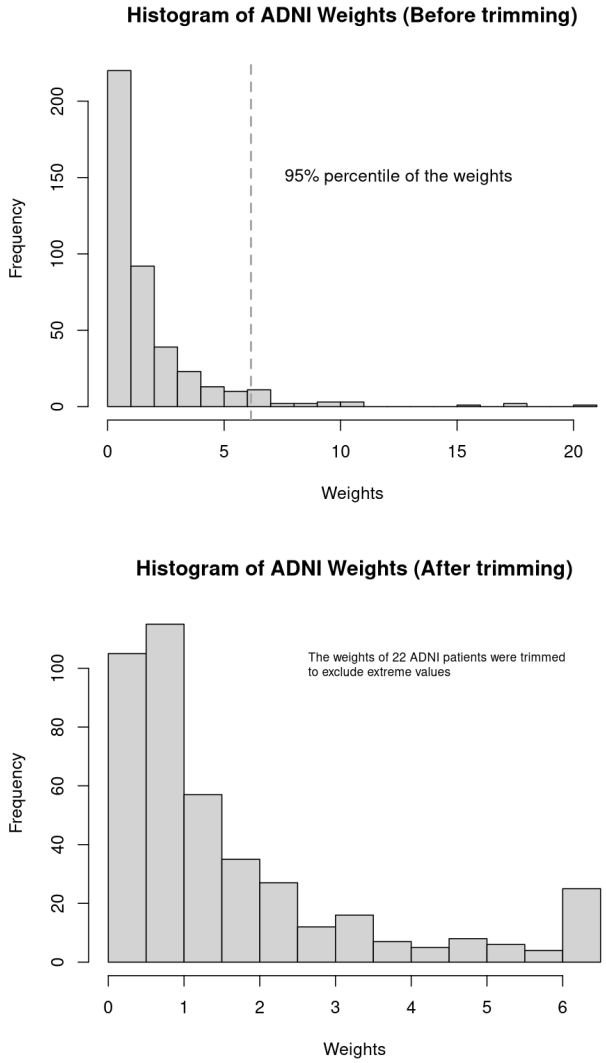
Figure 39 Population Before and After Weighting



Abbreviations: ADAS-Cog13, 13-Item Alzheimer's Disease Assessment Scale – Cognitive Subscale; APOEHOM, apolipoprotein E ε4 homozygote; CDR-SB, Clinical Dementia Rating – Sum of Boxes; MMSE, Mini-Mental State Exam

Source: Lilly Data on file, 2025

Figure 40 ADNI Weight Distributions Before and after Trimming in the EU SmPC population



Abbreviations: ADNI, Alzheimer's Disease Neuroimaging Initiative

Source: Lilly Data on file, 2025

Appendix Q. Transition probabilities from Potashman et al. 2021

An alternative data source for estimating transition probabilities is sourced from Potashman et al. 2021 (197). The study also used the NACC database through December 2017; however, it allowed participants to transition to health states that indicate improvement in cognition/function, which is inconsistent with the overall progressive nature of the disease. This aspect was constrained in the analysis used in the base-case analysis. Potashman et al. (2021) provides a transition matrix for all stages from asymptomatic to death for individuals with biomarker-confirmed (Aβ-positive) AD dementia pathology (197). The estimated annual progression rates were based on patient-level longitudinal data from the NACC UDS, which consisted of 3,291 incident patients and 4,370 prevalent patients from 2005 to 2017. The CDR-SB scores were used to define the AD dementia stage (0, 0.5–4.0, 4.5–9.0, 9.5–15.5, and 16.0–18.0 for asymptomatic, MCI due to AD, mild AD dementia, moderate AD dementia, and severe AD dementia, respectively) and to generate the transition probabilities. The study reported transition probabilities for incident and prevalent populations, and the authors indicated that the latter may have been overestimated when compared with the former because the time spent by the prevalent patients before entering the NACC data set may have been missed.

Because transition probability values for asymptomatic patients were not required in the model, the percentage transitioning to asymptomatic reported by Potashman et al. (2021) (197) was distributed proportionally to the remaining transition probabilities so that the transition probabilities from each health state summed up to 100%. In addition, the observed small regression probabilities were added to the probability of staying in the same state. Lastly, probabilities for transition to institutionalization were not reported in this study. The same approach for adjusting to 6-month cycle length and for obtaining transition probabilities to institutionalization as described above was employed for the transition probabilities reported in Table 98.

Table 98 Calculated 6-month Natural Full Transition Probability Matrix—Including Institutionalization from Potashman et al. (2021)

	To	Community				Institutionalized			
	From	MCI	Mild	Moderate	Severe	MCI	Mild	Moderate	Severe
Community	**MCI due to AD**	88.1%	8.7%	3.0%	0.1%	-%	-%	-%	-%
	Mild AD	–	77.9%	19.2%	2.4%	–	0.5%	0.1%	0.0%
	Moderate AD	–	–	75.1%	23.2%	–	–	1.3%	0.4%
	Severe AD	–	–	–	96.6%	–	–	–	3.4%
Institutionalized	**MCI due to AD**	–	–	–	–	88.1%	8.7%	3.0%	0.1%

Mild AD	–	–	–	–	–	78.3%	19.3%	2.4%
Moderate AD	–	–	–	–	–	–	76.4%	23.6%
Severe AD	–	–	–	–	–	–	–	100.0%

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

Source: Potashman et al. 2021 (197)

Appendix R. Transition probability matrix

Table 99 Calculated 6-month Natural Full Transition Probability Matrix—Including Institutionalization (NACC Analysis—CDR-SB)

	To	Community				Institutionalized			
	From	MCI	Mild	Moderate	Severe	MCI	Mild	Moderate	Severe
Community	**MCI due to AD**	84.8 %	14.3 %	0.7%	0.1%	-%	-%	-%	-%
	Mild AD	–	79.4 %	16.1%	1.5%	-%	2.5%	0.5%	0.0%
	Moderate AD	–	–	73.6%	18.4 %	–	–	6.4%	1.6%
	Severe AD	–	–	–	90.0 %	–	–	–	10.0%
Institutionalized	**MCI due to AD**	–	–	–	–	84.8 %	14.3 %	0.7%	0.1%
	Mild AD	–	–	–	–	–	81.9 %	16.6%	1.5%
	Moderate AD	–	–	–	–	–	–	80.0%	20.0%
	Severe AD	–	–	–	–	–	–	–	100.0 %

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

Note: The probability of progression to a more severe disease stage displayed in the disease progression model sheet in the cost-effectiveness model does not account for the probability of dying and it is also broken down by residential status, hence the values don't exactly match the ones displayed in the table above.

Source: Lilly, data on file, 2024 (118)

Appendix S. Justification for Confidential Information

Table 100 Justification for confidential information

Parameter	Justification
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]



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