SMC2871

donanemab concentrate for solution for infusion (Kisunla®)

Eli Lilly and Company Limited

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The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHSScotland. The advice is summarised as follows:

ADVICE: following a resubmission

donanemab (Kisunla®) is not recommended for use within NHSScotland.

Indication under review: for the treatment of mild cognitive impairment and mild dementia due to Alzheimer's disease (AD) in adult patients that are apolipoprotein E ε4 (ApoE ε4) heterozygotes or non-carriers.

In a randomised, double-blind, phase III study, donanemab reduced cognitive and functional decline associated with early Alzheimer's disease compared with placebo at 76 weeks.

The submitting company did not present a sufficiently robust clinical and economic analysis to gain acceptance by SMC.

Chair
Scottish Medicines Consortium

1. Clinical Context

1.1. Medicine background

Donanemab is a recombinant humanised immunoglobulin gamma 1 (IgG1) monoclonal antibody which selectively targets and binds specifically to a form of amyloid beta present only in brain amyloid plaques. Accumulation of these amyloid plaques is one of the defining features of Alzheimer's disease. The binding of donanemab to amyloid beta aids plaque removal through phagocytosis.[1]

The recommended dose of donanemab is 700 mg every 4 weeks for the first three doses, followed by 1,400 mg every 4 weeks via intravenous (IV) infusion. Treatment should be continued until amyloid plaques are cleared as confirmed using a validated method up to a maximum of 18 months. Treatment should be continued for up to 18 months if monitoring of amyloid plaque clearance with a validated method is not possible. If the patient progresses to moderate Alzheimer's disease before the end of the 18 months maximum treatment, donanemab should be stopped. Further details including monitoring requirements are included in the Summary of product characteristics (SPC).[1]

In order to promote the safe and effective use of donanemab, initiation of treatment in all patients should be through a central registration system implemented as part of a controlled access programme.[1]

1.2. Disease background

Alzheimer's disease is a progressive, neurological condition which is thought to be caused by an accumulation of proteins around brain cells. This includes beta amyloid which forms plaques and neurofibrillary tangles around brain cells disrupting neuron function. More than 90,000 people in Scotland are estimated to have dementia and Alzheimer's disease is the most common form of dementia, accounting for approximately 66% of cases.[2, 3]

Alzheimer's disease progresses through several stages: preclinical, mild cognitive impairment, mild dementia, moderate dementia and severe dementia due to Alzheimer's disease. The diagnosis of mild cognitive impairment can be inconsistent due to lack of guidance and furthermore can be challenging to attribute to Alzheimer's disease as early-stage symptoms can occur in many other clinical conditions. Recent Scottish Intercollegiate Guidelines Network (SIGN) guidelines define mild cognitive impairment due to Alzheimer's disease as "concern reflecting a change in cognition by the individual or an informant, with objective evidence of impairment in one or more cognitive domain, but with the preservation of independent functional abilities". Patients meeting this definition, in addition to having amyloid beta biomarkers on cerebrospinal fluid (CSF) immunoassay and neuronal injury on positron emission tomography (PET) scan, are the most likely to have mild cognitive impairment due to Alzheimer's disease.[2]

Dementia is typically characterised by memory impairment and in Alzheimer's disease is often accompanied by mental and behavioural symptoms. The SIGN guideline defines people with mild dementia as possibly able to live independently, but some supervision or support is often required. Judgement and problem solving are typically impaired but they may appear unimpaired to those who do not know them well.[2]

1.3. Treatment pathway and relevant comparators

There is currently no cure for Alzheimer's disease, but some medicines can relieve the symptoms including the acetylcholinesterase inhibitors (donepezil, galantamine and rivastigmine, which are licensed for the symptomatic treatment of mild to moderately severe Alzheimer's disease) and the N-methyl-D-aspartate antagonist (memantine, which is licensed for moderate to severe Alzheimer's disease). The National Institute for Health and Care Excellence (NICE) guideline recommends donepezil, galantamine or rivastigmine for mild to moderate Alzheimer's disease and these recommendations are endorsed by SIGN. There are no specific guidelines or recommendations for patients with mild cognitive impairment due to Alzheimer's disease. Psychological treatments, including cognitive stimulation therapy, may help to support the memory, problem solving skills and language. Lecanemab is an alternative monoclonal antibody licensed for the same indication as donanemab, however this has not been accepted for use by SMC (SMC2811).[2, 4, 5]

The submitting company considers best supportive care, including non-pharmacological management with or without symptomatic treatments, as the relevant comparator.

2. Summary of Clinical Evidence

2.1. Evidence for the licensed indication under review

Evidence to support the efficacy and safety of donanemab is from the phase III, randomised controlled study, TRAILBLAZER-ALZ 2 as detailed in Table 2.1.

Table 2.1. Overview of relevant study [1, 6, 7]

Criteria	TRAILBLAZER-ALZ 2
Study design	A randomised, double-blind, multicentre, phase III study
Eligible patients	• Adults aged 60 to 85 years inclusive with gradual and progressive change in memory function reported by the patient or informant for ≥ 6 months. • A MMSE score of 20 to 28 inclusive at screening. • Amyloid pathology (≥ 37 centiloids) and Tau pathology assessed by PET imaging. • Have a study partner (caregiver) who is in frequent contact with the patient (≥10 hours per week) and will accompany the patient to study visits or be available by telephone.
Treatments	Donanemab (700 mg for the first three doses and 1400 mg thereafter) or placebo, by intravenous infusion every 4 weeks for up to 72 weeks. If amyloid plaque level (assessed at 24 and 52 weeks) was < 11 centiloids on any single PET scan or < 25 but ≥ 11 centiloids on two consecutive PET scans, donanemab was switched to placebo in a double-blinded procedure. Symptomatic treatments for AD (including acetylcholinesterase inhibitors and memantine) were permitted during the study as background medication, provided that the dose had been unchanged for ≥ 30 days before randomisation.
Randomisation	Patients were randomised equally to donanemab or placebo. Randomisation was stratified according to investigative site and tau pathology (low to medium versus high).
Primary outcome	Change in iADRS score from baseline to week 76. The iADRS is an integrated assessment of cognition and daily function from the ADAS-Cog13 and ADCS-iADL measuring global disease severity across the AD continuum as a single summary score. Scores range from 0 to 144 with lower scores indicating greater impairment.

Selected secondary outcomes	Change from baseline to 76 weeks in: • CDR-SB: measures cognition and function across six categories (memory, orientation, judgement and problem solving, community affairs, home and hobbies, and personal care) by interviews with patients and caregivers. Scores range from 0 to 18 with higher scores indicating more impairment. • ADAS-Cog13: assesses areas of cognitive function across 13 items including orientation, verbal memory, language, praxis, delayed free recall, digit cancellation, and maze-completion measures. Scores range from 0 to 85 with higher scores indicating greater disease severity. • ADCS-iADL: assesses function with daily activities. Scores range from 0 to 59, with lower scores indicating greater disease severity. • Brain amyloid plaque deposition as measured by florbetapir or florbetaben F18 PET scan. Amyloid clearance was defined as < 24.1 centiloids.
Statistical analysis	Efficacy analyses were performed in the mITT (evaluable efficacy population), which included all patients who underwent randomisation with a baseline and at least one postbaseline efficacy measurement. A graphical testing scheme was applied in the study to the primary and selected secondary outcomes to control for multiplicity and type 1 error. Outcomes were tested in the low/medium tau population and combined (low/medium and high tau) population. The combined population is relevant for this submission. Natural cubic spline model and mixed-effect model for repeated measures statistical analyses were conducted for key outcomes. Results have been reported for the outcome analysis included in the graphical testing procedure only.

AD: Alzheimer's disease; ADAS-Cog13: 13-item Alzheimer's Disease Assessment Scale - Cognitive subscale; ADCS-iADL: Alzheimer Disease Cooperative Study—Instrumental Activities of Daily Living; CDR-SB: Clinical Dementia Rating Scale – Sum of Boxes; iADRS: integrated Alzheimer's Disease Rating Scale; mITT: modified intention-to-treat; MMSE: Mini-Mental State Examination; PET: positron emission tomography

Donanemab was associated with a statistically significant slowing of decline in integrated Alzheimer's disease Rating Scale (iADRS) scores at week 76 compared with placebo in the mITT population. A statistically significant benefit of donanemab over placebo was also observed with Clinical Dementia Rating Scale – Sum of Boxes (CDR-SB) scores, assessed as a key secondary outcome. The MHRA marketing authorisation excludes ApoE ε4 homozygous patients, resulting in a narrower indicated population.[1] A subgroup, with ApoEε4 homozygous patients excluded, referred to as the indicated population reflects the licence. Results for this subgroup were consistent with the mITT population and are shown in Table 2.2.

Table 2.2: Results for the primary and selected secondary outcomes from TRAILBLAZER-ALZ 2 [1, 6, 7]

	mITT population		**Indicated population[A]**	
	Donanemab (n=860)	**Placebo (n=876)**	**Donanemab (n=717)**	**Placebo (n=730)**
Primary outcome: Change from baseline to week 76 in iADRS[B]				
n/N (week 76/baseline)	583/775	653/824	NR	NR
Mean baseline iADRS	104.55	103.82	104.66	103.83
LSM change	-10.19	-13.11	-10.21	-13.59
LSM difference (95% CI), p-value	2.92 (1.51 to 4.33), p<0.001		3.38 (1.83 to 4.92)	
Key secondary outcome: Change from baseline to week 76 in CDR-SB[C]				
n/N (week 76/baseline)	598/794	672/838	NR	NR
Mean baseline CDR-SB	3.92	3.89	3.96	3.94
LSM change	1.72	2.42	1.67	2.43

LSM difference (95% CI), p-value	-0.70 (-0.95 to -0.45), p<0.001		-0.77 (-1.04 to-0.49)	
Key secondary outcome: Change from baseline to week 76 in ADCS-iADL[B]				
n/N (week 76/baseline)	591/780	661/826	NR	NR
Mean baseline ADCS-iADL	47.96	47.98	48.02	47.84
LSM change	-4.42	−6.13	-4.55	-6.31
LSM difference (95% CI), p-value	1.70 (0.84 to 2.57), p<0.001		1.76 (0.81 to 2.72)	
Key secondary outcome: Change from baseline to week 76 in ADAS-Cog13[B]				
n/N (week 76/baseline)	607/797	677/841	NR	NR
Mean baseline ADAS-Cog13	28.53	29.16	28.43	29.00
LSM change	5.46	6.79	5.37	7.06
LSM difference (95% CI), p-value	−1.33 (−2.09 to −0.57), p<0.001		-1.69 (-2.52 to -0.86)	
Key secondary outcome: Change in amyloid plaque deposition from baseline to week 76 on PET[C]				
n/N (week 76/baseline)	614/765	690/812		
Baseline amyloid centiloid	104.0	101.8	NR	NR
LSM change	-87.0	-0.7	-90.4	NR
LSM difference (95% CI), p-value	−86.4 (−88.9 to -83.9), p<0.001		NR	

ADAS-Cog13: 13-item Cognitive Subscale of the Alzheimer's Disease Assessment Scale; iADRS: integrated Alzheimer Disease Rating Scale; CDR-SB: Clinical Dementia Rating Scale-Sum of Boxes; CI: confidence interval; LSM: least squares mean; ; MMRM: mixed models for repeated measures; MMSE: Mini-Mental State Exam; PET: positron emission tomography; NCS2: natural cubic spline with 2 degrees of freedom; NR: not reported. [A]Indicated population includes adult patients with mild cognitive impairment or mild Alzheimer's Disease dementia who are ApoE ε4 heterozygotes or non-carriers [B]Calculated using NCS2 statistical methodology [C]Calculated using MMRM statistical methodology.

The submitting company provided data from a subgroup of patients referred to as the 'UK eligible subpopulation', which includes ApoE ε4 heterozygotes or non-carriers not taking an anticoagulant. They considered this subpopulation, which represents 75% of the mITT population (1310/1736), to be the most relevant population that reflects the UK licence and patients who would receive donanemab in clinical practice. Results in this subgroup were consistent with the mITT and indicated population; compared with placebo, donanemab showed: less decline in iADRS (least squares mean [LSM] difference 3.01 [95% CI: 1.41 to 4.61]), a smaller increase in CDR-SB (LSM difference -0.77 [95% CI: -1.07 to -0.48]), and a greater reduction in the mean brain amyloid plaque level at week 76. [8] This is the focus of the economic evaluation of this submission.

Exploratory time-based analyses suggest a lower risk of disease progression with donanemab treatment compared with placebo over the 18-month period based on iADRS (mITT population: hazard ratios [HR] 0.70, [95% CI: 0.58 to 0.84]; UK eligible subpopulation: HR 0.69 [95% CI: 0.55 to 0.86]), and CDR-SB (mITT population: HR 0.62 [95% CI: 0.52 to 0.75]; UK eligible subpopulation: HR 0.61 [95% CI: 0.49 to 0.76]).[6, 8] The results for CDR-SB for the UK eligible subpopulation have been used in the economic base case; the results for iADRS for the UK eligible subpopulation have been explored in alternative scenario analyses.

A descriptive time-saved analysis in the mITT population estimated that, at week 76, donanemab delayed disease progression versus placebo by 1.4 months on iADRS and 5.4 months on CDR-SB.[7]

2.2. Health-related quality of life outcomes

In TRAILBLAZER-ALZ 2, Health-Related Quality of Life (HRQoL) was assessed using the Quality of Life in Alzheimer's disease (QoL-AD) scale, which was completed by patients and caregivers. The scale has 13 items, each rated on a 4-point scale (poor, fair, good or excellent) and includes domains relating to mood, relationships, memory and finances. Points are totalled to give an overall score, with higher scores reflecting a better quality of life.[6, 9]

QoL-AD scores were similar between donanemab and placebo groups at baseline. By week 76, patient scores showed minimal change in both groups. Caregiver scores declined more in the placebo group, but the difference was not statistically significant.[10]

2.3. Supportive studies

TRAILBLAZER-ALZ was a phase II, randomised, double-blind study conducted in 257 patients with early symptomatic Alzheimer's disease (mild cognitive impairment due to Alzheimer's disease or mild Alzheimer's disease dementia) with amyloid and tau pathologies (patients with a high level of tau were not eligible for inclusion) who were randomised equally to receive donanemab or placebo. The primary outcome was change from baseline in iADRS at 76 weeks and the mean difference between the donanemab group and placebo group was 3.20 (95% confidence interval [CI]. 0.1 to 6.3), p=0.04. This was statistically significant. For the key secondary outcome of change in CDR-SB at 76 weeks from baseline, the difference between groups was not statistically significant (difference -0.4; 95% CI -0.8 to 0.1).[7, 11]

2.4. Indirect evidence to support clinical and cost-effectiveness comparisons

The long-term extension (LTE) phase of TRAILBLAZER-ALZ 2 was conducted to further evaluate donanemab efficacy and safety over time. Participants on donanemab during the double-blind phase who did not meet treatment completion criteria (based on amyloid PET) by week 76 continued donanemab treatment. Participants who did meet treatment completion criteria by week 76 switched to placebo at week 78. Participants initially randomised to placebo began donanemab at week 78.

Due to the lack of placebo arm beyond 18 months, the submitting company compared results from TRAILBLAZER-ALZ 2 LTE with weighted external data from the Alzheimer's Disease Neuroimaging Initiative (ADNI).

Table 2.3: Summary of the external cohort comparison

Criteria	Overview
Design	Propensity score-weighted comparison with a matched external control cohort. Baseline covariates included in the weighting procedure: age, sex, ApoE ε4 status (non-carrier or heterozygote), CDR-SB score, ADAS-Cog13, and MMSE score (at screening for TRAILBLAZER-ALZ 2 and at baseline for ADNI).
Population	- Patients from the TRAILBLAZER-ALZ 2 LTE UK eligible subpopulation (adult patients with mild cognitive impairment or mild dementia due to AD that are ApoE ε4 heterozygotes or non-carriers, who are not undergoing anticoagulant therapy). - UK indicated subpopulation of the ADNI cohort (cognitively impaired, amyloid-positive [assessed as having a cerebrospinal fluid total-tau/Aβ42 ratio >0.28], APOE ε4 heterozygotes and non-carriers with non-missing baseline covariates; no anticoagulant information recorded in ADNI). Before selecting the UK indicated population the ADNI

	included 2430 patients (cut-off date 10 January 2025); and after weighting to match the baseline characteristics of the placebo arm in the TRAILBLAZER-ALZ 2 trial, the sample size was considerably reduced.
Comparators	Donanemab-treated patients (including those who discontinued treatment at 6, 12 or 18 months or continued beyond 18 months) versus untreated weighted ADNI cohort.
Studies included	TRAILBLAZER-ALZ 2 LTE trial [12] and the ADNI multicentre, observational study [13]
Outcomes	Change from baseline in CDR-SB score up to 36 months.
Results	The 95% CI for the difference in CDR-SB did not include 0, so the evidence suggests that donanemab reduced cognitive decline on the CDR-SB scale at 36 months compared with the ADNI-weighted cohort. An analysis excluding patients who received donanemab for more the 18 months showed consistent results. Sensitivity analyses generally showed consistent results across various methods and subpopulations. However, when the amyloid centiloid level variable was added in the propensity score calculation, the 95% CI for the difference in CDR-SB scores included 0, suggesting no evidence of a difference between donanemab and the ADNI-weighted cohort at 36 months.

AD: Alzheimer's disease; ADAS Cog13: 13-item Cognitive Subscale of the Alzheimer's Disease Assessment Scale; ADNI: Alzheimer's Disease Neuroimaging Initiative; ApoE ε4: apolipoprotein E ε4; CDR-SB: Clinical Dementia Rating Scale-Sum of Boxes; CI: confidence interval; LTE: long-term extension; LSM: least squares mean; MMSE: Mini-Mental State Exam.

*Other data were also assessed but remain confidential.**

3. Summary of Safety Evidence

In TRAILBLAZER-ALZ 2 safety population, 853 patients received donanemab and 874 received placebo; any treatment-emergent adverse event (AE) was reported by 89% (759/853) of patients in the donanemab group and 82% (718/874) in the placebo group; patients with a reported serious AE were 17% versus 16%, and patients discontinuing therapy due to an AE was 13% versus 4.3%.[6]

The most frequently reported treatment-emergent AEs with an incidence >5% in the donanemab group versus the placebo group were: amyloid-related imaging abnormalities of oedema or effusions (ARIA-E) (24% versus 1.9%), amyloid-related imaging abnormality of microhaemorrhages and hemosiderin deposits (ARIA-H) (20% versus 7.4%), COVID-19 (16% versus 18%), headache (14% versus 9.8%), fall (13% in both groups), infusion-related reactions (8.7% versus 0.5%), superficial siderosis of central nervous system (6.8% versus 1.1%), dizziness (6.2% versus 5.5%), arthralgia (5.7% versus 4.8%), urinary tract infection (5.3% versus 6.8%), diarrhoea (5.0% versus 5.7%) and fatigue (4.9% versus 5.1%).[6]

Amyloid-related imaging abnormalities (ARIAs) were an AE of special interest. ARIA-E most commonly cause swelling in areas of the brain and ARIA-H cause small spots of bleeding in or on the surface of the brain. Most ARIA radiographic events occurred within 24 weeks of initiating donanemab however they can occur at any time and patients can have multiple events. In a pooled analyses of TRAILBLAZER-ALZ and TRAILBLAZER-ALZ 2, in the indicated population (excluding ApoE ε4 homozygous patients), ARIA-E were observed in 21% (170/816) of the

donanemab group and 1.6% (13/825) of the placebo group. These were symptomatic in 5.4% of patients treated with donanemab and 1.7% of events were considered severe, the median time to resolution was approximately 9 weeks. ARIA-H were observed in 27% in the donanemab group and 12% in the placebo group in the pooled analyses. These were symptomatic in 1.0% of patients treated with donanemab and 7.5% of events were considered severe. ARIA-H without the presence of ARIA-E occurred in a similar proportion of patients in each group (12% versus 11%).[1]

Intracerebral haemorrhage measuring > 1 cm was reported by 0.4% in the donanemab group and 0.2% in the placebo group.[6]

In TRAILBLAZER-ALZ 2 placebo-controlled phase, 3 deaths were considered related to donanemab treatment, and one was considered related to treatment in the placebo group. The treatment-related deaths in the donanemab group were related to serious ARIAs, and in the placebo group it was due to arteriosclerosis.[6]

The SPC provides recommendations for monitoring and managing ARIAs. It also recommends that donanemab should not be initiated in patients receiving ongoing anticoagulant therapy.[1]

*Other data were also assessed but remain confidential.**

4. Summary of Clinical Effectiveness Considerations

4.1. Key strengths

- In TRAILBLAZER-ALZ 2, donanemab slowed cognitive and functional decline over 76 weeks compared with placebo, with a statistically significant mean iADRS difference of 2.92 in the mITT population.[6, 7]
- The key secondary outcome, CDR-SB, also showed a statistically significant benefit (mean difference: -0.70 in the mITT population at 76 weeks), alongside other key secondary outcomes (such as ADCS-iADL, ADAS-Cog13, amyloid plaque) favouring donanemab over placebo.[6, 7]
- In the indicated population (excluding ApoE ε4 homozygotes), mean numerical differences were 3.38 for iADRS and -0.77 for CDR-SB.[1] Results in the UK eligible subpopulation (excluding ApoE ε4 homozygotes and anticoagulant users) were broadly consistent.[8]
- Uncontrolled data from the LTE of TRAILBLAZER-ALZ 2 suggest a maintenance of effect over 3 years. [14]

4.2. Key uncertainties

- The submitting company provided evidence from descriptive post-hoc analyses excluding ApoE ε4 homozygotes and anticoagulant users, aiming to reflect the population most likely to receive donanemab in clinical practice. This approach follows findings from TRAILBLAZER-ALZ 2, where ApoE ε4 homozygotes (17% of the mITT population) showed reduced efficacy and increased risk of ARIA, leading to their exclusion from the marketing authorisation. Additionally, the SPC advises against use with anticoagulants due to risks of ARIA-H and intracerebral haemorrhage. The study was not powered to detect differences between subgroups. [6-8]

- The effects of donanemab on both iADRS and CDR-SB scales appear modest, and their clinical relevance remains uncertain.
    - As noted in the MHRA public assessment report, while donanemab significantly reduces amyloid beta plaque and demonstrated statistically significant results in both primary and key secondary outcomes, it remains to be established whether this reduction translates into a clinically meaningful benefit for patients with early-stage Alzheimer's disease.[7]
    - In TRAILBLAZER-ALZ 2, results show only approximately 3-point difference between groups in iADRS (an outcome developed by the submitting company with total scores ranging from 0 to 144; although the submitting company notes this scale covers the full disease spectrum of Alzheimer's disease and only a sub-section of iADRS reflects the early symptomatic patient population). Descriptive analyses suggested a delay in disease progression based on iADRS of 1.4 months with donanemab over a period of 18 months; this delay may not be clinically meaningful at this early stage in this chronic illness. It is also unclear which item or domain may have driven the iADRS score.[6, 15]
    - CDR-SB is an established outcome in clinical studies, however its minimal clinically important difference remains heavily debated.[16] The clinical relevance of CDR-SB scores in an overall population is difficult to interpret for individual patients and could vary according to the stage and trajectory of disease and the magnitude of decline. Although a broad slowing of progression was observed in all domains, the individual benefit for patients will differ depending on which domain is more affected in practice.[6]
    - The submitting company argue donanemab benefits, with approximately 22% and 29% slowing of clinical decline on the iADRS and CDR-SB scales, are clinically meaningful. However, it remains uncertain whether this translates into a meaningful impact on cognition, daily functioning, or quality of life of patients and their families. Notably, the HRQoL outcome from TRAILBLAZER-ALZ 2 showed no significant differences between groups at 76 weeks for patients or caregivers. Clinical experts consulted by SMC noted that the iADRS and CDR-SB scales are not used in clinical practice, and expressed differing views on whether a >20% change on these scales could be considered clinically meaningful. Determining a threshold for clinical relevance is challenging, particularly given the heterogeneity in disease presentation and progression patterns observed in Alzheimer's disease.
- Placebo-controlled data for donanemab are limited to 18 months. Beyond this, longer-term extension findings, extending to 3 years, rely on comparisons with the ADNI external cohort. The submitting company claim this comparison demonstrates a sustained treatment effect beyond the initial 18-month study period and supports the cost-effectiveness modelling approach.Results suggest slower clinical decline in donanemab-treated patients. However, several limitations affect the robustness and generalisability of these results. These include residual confounding, missing data (for example amyloid centiloid levels), population differences (for example anticoagulant use), small sample size, and reliance on a single score comparison (CDR-SB). Notably, some patients received donanemab beyond the SPC's recommended 18-month duration. Despite the limitations, the methodology appears

appropriate and the sensitivity analyses comprehensive. While the results remain uncertain, they do offer some reassurance regarding the potential maintenance of effect.

- Clinical experts consulted by SMC highlighted that the incidence and substantial risk of ARIA events are of particular concern. To address safety concerns, the MHRA has requested a post-authorisation study to monitor ARIAs, intracerebral haemorrhage, and long-term safety. A controlled access programme will also be implemented to collect UK prescribing and AEs. [6, 7]
- The degree of cognitive impairment at screening was categorised based on MMSE score; a score of ≥27 defined mild cognitive impairment and a score of 20 to 26 defined mild Alzheimer's disease. Although MMSE is less commonly used now, clinical experts consider these categories reasonable. In TRAILBLAZER-ALZ 2, 17% of patients in the donanemab group had mild cognitive impairment and 83% had mild Alzheimer's disease (16% and 84% in the UK eligible subpopulation).[6, 8] It is uncertain if this is reflective of patients in Scotland who would be offered donanemab if available and how diagnosis in this population could evolve over time.
- In TRAILBLAZER-ALZ 2, 61% of patients were on symptomatic treatment (acetylcholinesterase inhibitors and/or memantine). Subgroup analyses showed donanemab was beneficial regardless of baseline treatment, though the iADRS benefit was smaller in those not on symptomatic therapy (adjusted mean difference 1.20).[6] This may affect the generalisability of results, since no symptomatic treatments are currently licensed for mild cognitive impairment and memantine is only licensed for the treatment of moderate or severe Alzheimer's disease, although there may be off-label use.
- Blinding in TRAILBLAZER-ALZ 2 may have been affected by infusion reactions and ARIA events, potentially biasing subjective outcomes. To mitigate this, CDR-SB raters were blinded to AE data. Sensitivity analyses censoring scores after ARIA or infusion reactions aligned with the primary analysis, supporting donanemab's benefit.[6]

4.3. Clinical expert input

Clinical experts consulted by SMC considered that donanemab could potentially fill an unmet need in early Alzheimer's disease as there are no disease modifying treatments currently available. Expert opinion regarding whether donanemab represented a therapeutic advance was mixed with some caution expressed regarding the magnitude of benefit and safety risks.

4.4. Service implications

Diagnostic test required to identify patients eligible for treatment: contact local laboratory for information.

To identify eligible patients, PET scans or CSF analysis or equivalent validated methods is required to confirm beta amyloid pathology. In addition, genetic testing of ApoE ε4 phenotype to confirm heterozygous or non-carrier status is required to meet the marketing authorisation. Brain magnetic resonance imaging (MRI) scans are needed before starting donanemab and during treatment, as detailed in the SPC, to monitor for potential ARIA-E and ARIA-H. These diagnostic tests and MRI access are expected to have a substantial impact on services. The administration of donanemab requires IV infusion every 4 weeks and this has implications for patients, carers and

the service. Clinical experts consulted by SMC highlighted that these requirements would have major service implications, and that considerable additional clinical capacity would be required to introduce donanemab into practice.

5. Summary of Patient and Carer Involvement

The following information reflects the views of the specified Patient Groups.

- We received patient group submissions from Alzheimer's Research UK, Alzheimer Scotland and Dementia UK. All three organisations are registered charities.
- Alzheimer's Research UK has received 0.06% pharmaceutical company funding in the past two years, including from the submitting company. Alzheimer Scotland has received 0.59% pharmaceutical company funding in the past two years, with none from the submitting company. Dementia UK has not received any pharmaceutical company funding in the past two years.
- Each person's experience of mild cognitive impairment (MCI) due to Alzheimer's disease and early-stage Alzheimer's is different and unique, many find everyday activities like going to the shops, remembering appointments, and managing bills and letters difficult. It also has a distinct impact on loved ones, many of whom take up the role of informal carer. As the disease progresses to more advanced stages, the burden on care partners increases substantially. In addition to physical symptoms, carers manage difficult changes in their loved ones' behaviour and personality.
- There are currently a few licensed medications available for the treatment of the symptoms of Alzheimer's disease. The effectiveness of the medications available is variable, they can have side effects and do not work for everybody. None of these treatments address the underlying causes of Alzheimer's disease.
- Donanemab is one of a new class of treatment for mild cognitive impairment due to Alzheimer's disease which could alter the natural course of the condition.
- Donanemab may bring improvements to the quality of life for those with mild to moderate Alzheimer's disease, such as slowing the progression of the condition and providing more time to plan for the future.
- Donanemab gives patients and their families hope for the future. However, there are concerns about the negative side effects and safety concerns of this treatment which would require close monitoring.

6. Summary of Comparative Health Economic Evidence

6.1. Economic case

The economic case is summarised in Table 6.1.

Table 6.1 Description of economic analysis

Criteria	Overview
Analysis type	Cost-utility analysis
Time horizon	28 years, assuming a starting age of 73 years
Population	The economic analysis was conducted in the UK eligible subpopulation of patients with mild cognitive impairment (MCI) or mild Alzheimer's disease (AD), who are ApoE ε4 heterozygotes or non-carriers and who are not using an anticoagulant.
Comparators	Donanemab was considered as an add-on therapy to best supportive care (BSC). BSC was also the only included comparator. BSC consisted of the pharmacological interventions acetylcholinesterase inhibitors and memantine. Non-pharmacological interventions were not explicitly included, with the submitting company arguing that these are low cost and used equally across arms and therefore would not be impactful upon the economic results.
Model description	The analysis used a Markov model, which traced the progression of AD across patients' life span. The included health states were MCI due to AD, mild AD, moderate AD, severe AD and death. CDR-SB score was used to define health states. Each of the health states were subdivided into substates to capture whether patients were receiving care in community or institutional settings. All patients started in the MCI due to AD or mild AD states. The distribution of patients across those starting states was based on the observed proportions in the UK controlled access programme for donanemab. In the base case 79.5% of patients started in the MCI state and 20.5% of patients started in the mild state. A six-month cycle length was used, with a half-cycle correction applied.
Clinical data	The central source of clinical evidence was the TRAILBLAZER-ALZ 2 study.[1, 6, 7] The treatment effect across the study period was estimated using the hazard ratio of disease progression for donanemab compared to BSC.
Extrapolation	The risk of progression in each of the states within the BSC arm of the model was estimated from National Alzheimer's Coordinating Centre (NACC) data using a multinomial logistic regression. Transitions in the donanemab arm were based on the same transitions used in the BSC arm, estimated from the NACC data. These were adjusted based on a time dependent treatment effect. For patients who received a full course of donanemab treatment, either across 18-months or having successfully achieved amyloid clearance at 6 or 12 months, the full treatment effect estimated from the TRAILBLAZER-ALZ 2 study was assumed to hold up until 5.5 years. This was the point at which the submitting company estimated that amyloid plaque levels would reach 24.1 centiloids. A waning period was assumed, with no treatment effect after 14.5 years post-treatment initiation, at which amyloid plaque levels would be around 50 centiloids. When the treatment effect of donanemab was lost, patients were subject to the same probability of progression as patients in the BSC arm. Patients would discontinue donanemab early if they progressed to moderate or severe disease or experienced adverse events which necessitated stopping treatment. In the event of these early discontinuations, patients were assumed to retain full treatment effect for 12 months, with treatment waning over a further 2.5 years, and no treatment effect applied after 3.5 years. The risk of institutionalisation was based on an external source, with no risk assumed in the MCI state.[17] Mortality was modelled separately to progression risk. The hazard ratio of death for each disease state was estimated relative to the MCI state, based on NACC data. The company

	assumed that the MCI group had a mortality rate equal to that of the age matched general population and so applied the hazard ratio to model death in each of the disease states.
Quality of life	No data suitable for modelling health-related quality of life in the economic model were collected as part of the TRAILBLAZER-ALZ 2 study. Instead, the analysis relied on external sources. Utility in the MCI state was assumed to be equal to that of the general population (0.76). Values for mild AD (0.74), moderate AD (0.59) and severe AD (0.36) were drawn from Landeiro et al (2020).[18] Utility values for patients in institutional settings were assumed the same as those in the community setting. Disutilities were applied for adverse events. Due to significant carer burden that can result from AD, the submitting company chose to explore carer health impacts in scenario analysis (See Section 6.3). Utilities of carers for patients in the MCI, mild and moderate AD states were estimated by the submitting company using a vignette study. Health states were valued using a time trade off method, based on interviews with 304 individuals in the UK. The utility value for carers of patients in the severe state was estimated by adjusting the moderate utility from the company study by the difference in utilities for carers of patients in moderate and severe states reported in Belger et al. (2022).[19]
Costs and resource use	Medicine costs included in the model were diagnostic testing costs, acquisition costs, administration costs and adverse event costs. Wider NHS and social care costs included monitoring costs, from MRI scans and health state resource costs that looked to capture all other relevant costs of AD management.
PAS	A Patient Access Scheme (PAS) was submitted by the company and assessed by the Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation in NHSScotland. Under the PAS, a discount was offered on the list price.

6.2. Results

The economic analysis estimated that treatment with donanemab led to higher acquisition costs but also better health outcomes for the patient by maintaining them in the less severe health states for longer. The results, inclusive of the PAS discount on donanemab, are presented in Table 6.2.

Table 6.2 Baseline results (inc. of PAS on donanemab)

Technologies	Total costs (£)	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER (£/QALY)
Donanemab	*CiC*	5.23	-	-	-	-
BSC	*CiC*	4.67	£5,088	0.38	0.56	£9,020

Abbreviations: CiC: commercial in confidence; ICER: incremental cost-effectiveness ratio; Incr.: Incremental; LYG: life years gained; QALY: quality-adjusted life year.

6.3. Sensitivity analyses

The company conducted one-way sensitivity analysis, probabilistic sensitivity analysis and scenario analysis to explore uncertainty. A selection of scenarios is presented in Table 6.3. These are inclusive of the PAS discount on donanemab.

Table 6.3 Scenario analysis (inc. of PAS on donanemab)

	Parameter	Base case	Scenario	Incr. costs (£)	Incr. QALYs	ICER (£/QALY)
	Base case	-	-	5,088	0.56	9,020
1	Time horizon	28 years	20 years	4,838	0.56	8,637

2	Starting population	79.5% MCI due to AD and 20.5% mild dementia due to AD	100% MCI due to AD	3,740	0.60	6,218
3			100% mild dementia due to AD	10,322	0.42	24,637
4			aligned to UK eligible population in TRAILBLAZER-ALZ 2 study: 21.2% MCI, 78.8% mild	8,926	0.46	19,505
5	Treatment duration	Fixed duration (18 months) or treat-to-clear	Fixed duration of treatment only	5,446	0.56	9,655
6			Treat-to-clear only	1,493	0.56	2,646
7	Treatment effect	Hazard ratio estimated from TRAILBLAZER-ALZ 2 study	Upper 95% confidence interval	10,870	0.31	34,552
8			Lower 95% confidence interval	-472	0.79	Dominant*
9	Treatment effect estimate	CDR-SB score	iADRS score	8,209	0.43	19,038
10	Stopping rules	Treatment stops at movement to moderate or severe AD	Treatment stops at movement to severe AD	*CiC*	*CiC*	*CiC*
11	Transition probabilities	NACC	Potashman et al (2021)[20]	4,354	0.57	7,656
12	Caregiver utilities	Excluded	Included (1.8 carers per patient)	5,088	0.99	5,136
13			Included (1.0 carers per patient)	5,088	0.80	6,351
14	Waning effect	Full treatment effect of donanemab is applied up to 5.5 years. A linear waning effect is then applied with no treatment effect remaining at year 14.	Increased duration of full treatment effect – up to 7.5 years (threshold of amyloid-positive increased to 30 CL)	4,639	0.60	7,767
15			Faster treatment waning – no treatment effect by year 12.5 (no treatment effect remaining at an amyloid plaque level of 43.69 CL)	5,368	0.54	9,971
16			Faster treatment waning – no treatment effect by year 10.5 (no treatment effect remaining at an	5,617	0.52	10,848

			amyloid plaque level of 38.09 CL)			
	Combined scenarios					
17	• 20-year time horizon (Scenario 1) • Patient mix matched to TRAILBLAZER-ALZ 2 (Scenario 4) • Fixed duration of treatment (Scenario 5)			9,092	0.46	19,946
18	• 20-year time horizon (Scenario 1) • 100% mild dementia (Scenario 3) • Fixed duration of treatment (Scenario 5) • iARDS treatment effect estimate (scenario 9)			11,741	0.31	37,593
19	• 20-year time horizon (Scenario 1) • 100% mild dementia (Scenario 3) • Fixed duration of treatment (Scenario 5) • iARDS treatment effect estimate (scenario 9) • Include carer utilities - 1.8 carers per patient (Scenario 12)			11,741	0.59	19,974

Abbreviations: AD: Alzheimer's disease; ICER: incremental cost-effectiveness ratio; Inc.: Incremental; MCI: mild cognitive impairment; NACC: National Alzheimer's Coordinating Centre; PSSRU: Personal Social Services Research Unit; QALY: quality-adjusted life year
* Dominant: The assessed medicine was estimated as having lower costs and greater health outcomes than the comparator.

6.4. Key strengths

- The choice of comparator seemed appropriate. While there was some uncertainty over whether the use of acetylcholinesterase inhibitors and memantine across Alzheimer's disease severity matched Scottish clinical practice, the limited efficacy and low cost of these medicines meant impact upon the economics was likely to be small. The exclusion of non-pharmacological interventions appeared reasonable.
- The model structure appeared appropriate and had good alignment with previous SMC submissions in this disease area.

6.5. Key uncertainties

- State occupancy in the model was defined based on the CDR-SB instrument. This was not the primary endpoint of the TRAILBLAZER-ALZ 2 study, which was iADRS. The submitting company argued that the CDR-SB is commonly used in Alzheimer's disease research and facilitated linking with external data sources, however, this was seen as a source of uncertainty. The choice to use the CDR-SB introduced discrepancy between the clinical and economic evidence and it was noted that CDR-SB was a less granular instrument which may perform more poorly at capturing the scale of the treatment effect. Further, while CDR-SB is a recognised measure of cognitive and functional decline, this instrument is not commonly used as a diagnostic or monitoring tool in Scotland. This may mean that modelled outcomes differ from those which would be expected in Scotland. The scale and direction of any bias introduced is unknown. The company has provided a scenario using the iADRS to estimate the scale of the treatment effect and this led to an increase in the incremental cost-effectiveness ratio (ICER) (See Scenario 9, Table 6.3)
- The model assumed that of the patients starting donanemab, 79.5% would have mild cognitive

impairment due to Alzheimer's disease, while 20.5% would have mild Alzheimer's disease, aligned with real-world data of donanemab use in the UK up to July 2025. Later data collected up to November 2025 increased the proportion of patients with mild cognitive impairment due to Alzheimer's disease to 85.1%, although modelling was not updated to reflect this. Given the complexities in diagnosing and initiating patients on donanemab, the starting proportions were seen as uncertain and subject to change over time. Feedback received by SMC from Scottish clinicians was not definitive on what patients were most likely to receive treatment, and patients included in the TRAILBLAZER-ALZ 2 study predominantly had mild disease. The spilt between having mild cognitive impairment due to Alzheimer's disease and mild Alzheimer's disease had an impact upon the ICER (Scenarios 2 to 4).

- There was some uncertainty over whether the slowed progression observed from donanemab treatment in the TRAILBLAZER-ALZ 2 study was clinically meaningful. Despite this, the model projects quality of life and longevity gains for donanemab treatment. A related area of concern were the assumptions related to treatment waning. The company supported their assumptions based on the level of amyloid plaque at the end of the treatment period, the rate of return from external sources and the persistence of treatment effect seen in the TRAILBLAZER-ALZ 2 LTE study, with alternative assumptions explored (Scenarios 14 to 16). However, the approach is based on an implied assumption that amyloid plaque levels are a key prognostic factor in Alzheimer's disease severity. Alzheimer's disease is a complex disease with a number of drivers, meaning that the waning assumptions are uncertain. Overall, it was unclear whether the model accurately reflected the expected outcomes for Alzheimer's disease patients with or without donanemab treatment.
- Progression between health states in the model were based on annual transitions estimated from patients in the NACC database. The data collection points in the NACC database were annual, meaning that only annual transitions could be directly estimated. The model used a 6-month cycle length to align with the clearance testing points of the TRAILBLAZER-ALZ 2 study. As a result, within the model, the estimated annual transitions were disaggregated into 6-month transition probabilities. This double application of those 6-month probabilities does not necessarily result in consistent dynamics with the original source. This could have exaggerated the estimated cost-effectiveness of donanemab by artificially inflating the incremental health benefits while deflating the incremental costs. The submitting company stated that they assessed the scale of any introduced bias as small. Further, the submitting company noted that an alternative data source was explored in scenario analysis with minimal impact on the economic results (Scenario 11). However, this source also used data from the NACC database and similarly estimated annual transition probabilities, so was not seen as suitably addressing the uncertainty.
- The submitting company assumed that patients would stop when they transition to moderate or severe disease. Despite this rule being prescribed in the SPC, there was some uncertainty whether all patients would discontinue treatment at this point, particularly as the manner that disease stage is defined between the model and Scottish clinical practice may differ. Upon request, the submitting company provided a scenario exploring the implications of treatment with donanemab extending until severe disease (Scenario 10). This had a very moderate

impact upon the ICER. Because discontinuation at transition to the moderate disease is written into the SPC, the submitting company considered this scenario inappropriate for decision making and so has classed the result as commercial in confidence.

7. Conclusion

After considering all the available evidence, the Committee was unable to accept donanemab for use in NHSScotland.

8. Guidelines and Protocols

The Scottish Intercollegiate Guidelines Network (SIGN) published a national clinical guideline SIGN 168: Assessment, diagnosis, care and support for people with dementia and their carers, in November 2023.[2]

The National Institute for Health and Care Excellence (NICE) published NICE guideline 97: Dementia: assessment, management and support for people living with dementia and their carers, in June 2018.[4]

9. Additional Information

9.1. Product availability date

January 2025

Table 9.1 List price of medicine under review

Medicine	Dose regimen	Cost per 18 months (£)
donanemab	**700 mg every 4 weeks for the first three doses, followed by 1400 mg every 4 weeks via IV infusion. Treatment should be continued for a maximum of 18 months**	**42,952**

Costs from BNF online on 30 October 2025. Costs calculated using the full cost of vials/ampoules assuming wastage. Costs do not take any patient access schemes into consideration.

10. Company Estimate of Eligible Population and Estimated Budget Impact

The submitting company estimated there would be 422 patients eligible for treatment with donanemab in year 1 and 2,151 patients in year 5. The estimated uptake rate was 11% in year 1 and 47% in year 5 with no discontinuation rate applied. This resulted in 47 patients estimated to receive treatment in year 1 rising to 1,014 patients in year 5, inclusive of patients remaining on treatment from one year to the next.

SMC is unable to publish the with-PAS budget impact due to commercial in confidence issues.

*Other data were also assessed but remain confidential.**

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This assessment is based on data submitted by the applicant company up to and including 12 December 2025.

**Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal:*https://www.scottishmedicines.org.uk/about-us/policies-publications/

Medicine prices are those available at the time the papers were issued to SMC for consideration. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

Patient access schemes: A patient access scheme is a scheme proposed by a pharmaceutical company in order to improve the cost-effectiveness of a medicine and enable patients to receive access to cost-effective innovative medicines. A Patient Access Scheme Assessment Group (PASAG), established under the auspices of NHS National Services Scotland reviews and advises NHSScotland on the feasibility of proposed schemes for implementation. The PASAG operates separately from SMC in order to maintain the integrity and independence of the assessment process of the SMC. When SMC accepts a medicine for use in NHSScotland on the basis of a patient access scheme that has been considered feasible by PASAG, a set of guidance notes on the operation of the scheme will be circulated to Area Drug and Therapeutics Committees and NHS Boards prior to publication of SMC advice.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.