SMC2687

donanemab concentrate for solution for infusion (Kisunla®)

Eli Lilly and Company Limited

04 April 2025

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 full submission

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.

The submitting company has indicated their intention to make a resubmission.

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.[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 62% 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 (SMC2700).[2, 4, 5]

The submitting company considers best supportive care (BSC), 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-ALZ2 as detailed in Table 2.1.

Table 2.1. Overview of relevant studies[6, 7]

Criteria	TRAILBLAZER-ALZ2
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-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 key 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 carer giver. Scores range from 0 to 18 with higher scores indicating more impairment. • ADAS-Cog_{13}: assessing areas of cognitive function across 13 items including orientation, verbal memory, language, praxis, delayed free recall, digit cancellation, and maze-completion measures. Scores ranges 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-Cog_{13}: 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

In the TRAILBLAZER-ALZ2 study, treatment with donanemab was associated with a statistically significant smaller reduction in integrated Alzheimer's Disease Rating Scale (iADRS) at week 76 compared with placebo in the mITT population. The submitting company indicated this represents a 22% slowing of disease progression as measured by iADRS. The decline in key secondary outcome, Clinical Dementia Rating Scale – Sum of Boxes (CDR-SB) at week 76 was also statistically significantly smaller in the donanemab group compared with the placebo group in the mITT population. However, the MHRA marketing authorisation for donanemab is narrower than the overall mITT population as it excludes ApoEε4 homozygous patients. A subgroup, with ApoEε4

homozygous patients excluded, referred to as the indicated population reflects the licence. Results from this population were similar to the mITT population and are presented in Table 2.2.[1, 6, 7]

Table 2.2: Results for the primary and selected key secondary outcomes from the TRAILBLAZER-ALZ2 study in the mITT and indicated populations. [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	2.92 (1.51 to 4.33), p<0.001		3.38 (1.83 to 4.92)	
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)	-0.70 (-0.95 to -0.45), p<0.001		-0.77 (-1.04 to-0.49)	
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)	1.70 (0.84 to 2.57), p<0.001		1.76 (0.81 to 2.72)	
Secondary outcome: Change from baseline to week 76 in ADAS Cog_{13}[B]				
n/N (week 76/baseline)	607/797	677/841	NR	NR
Mean baseline ADAS Cog_{13}	28.53	29.16	28.43	29.00
LSM change	5.46	6.79	5.37	7.06
LSM difference, (95% CI)	−1.33 (−2.09 to −0.57), p<0.001		-1.69 (-2.52 to -0.86)	
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)	−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; MCI: mild cognitive impairment; 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 MCI or mild AD dementia who are APOE E4 heterozygotes or non-carriers [B]Calculated using NCS2 statistical methodology [C]Calculated using MMRM statistical methodology.

The submitting company provided results from a subgroup of patients referred to as the UK eligible population that included patients who are ApoEε4 heterozygotes or non-carriers and those not using an anticoagulant. They considered this was the most relevant population to reflect the licence and patients who would receive donanemab in clinical practice. The results from the UK eligible population were consistent with the indicated population. Treatment with donanemab resulted in a smaller reduction in iADRS and a smaller increase in CDR-SB compared with placebo at week 76. Donanemab was also associated with a greater decrease in amyloid plaque deposition at week 76.[8]

Hazard ratios (HRs) for risk of disease progression were derived based on iADRS (mITT population: HR 0.70, [95% CI: 0.58 to 0.84]),and CDR-SB (mITT population: HR 0.62 [95% CI: 0.52 to 0.75]).[6, 8] The results for CDR-SB for the UK eligible population have been used in the economic base case.

A time-saved analyses was conducted as a descriptive secondary outcome in the mITT population to evaluate if donanemab could slow disease progression and delay the development of a subsequent more severe stage of disease. At week 76 compared with placebo, donanemab delayed disease progression by 1.4 months on the iADRS and by 5.4 months on the CDR-SB scale in the overall study population.[7]

2.2. Health-related quality of life outcomes

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]

The QoL-AD scale was completed by a subset of patients from the TRAILBLAZER-ALZ2 study. At baseline the patient-reported QoL-AD score was similar in both the donanemab and placebo groups with minimal change at week 76 in either group. At baseline, the caregiver QoL-AD score was similar in both treatment groups, there was a greater reduction in the score of the placebo group at week 76 compared with the donanemab group however the between group 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 [MCI] 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]. 0.12 to 6.27), p=0.04. This was statistically significant. For the key secondary endpoint 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]

TRAILBLAZER-ALZ 4 was a phase III, open-label study conducted in 148 patients with early symptomatic Alzheimer's disease who were randomised equally to receive donanemab or aducanumab. A greater percentage of patients treated with donanemab reached amyloid plaque clearance (less than 24.1 centiloids) on florbetapir F18 PET scan at 6 months compared with aducanumab (38 % versus 1.6 %). A comparable reduction in amyloid was observed regardless of baseline tau presence.[1]

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

3. Summary of Safety Evidence

In the TRAILBLAZER-ALZ 2 study, 853 patients received donanemab and 874 received placebo in the safety population; any treatment-emergent adverse event (TEAE) 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 TEAEs of any severity 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]

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-ALZ2, in the indicated population (excluding ApoEε4 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 > 1cm was reported by 0.4% in the donanemab group and 0.2% in the placebo group.[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]

4. Summary of Clinical Effectiveness Considerations

4.1. Key strengths

- In the TRAILBLAZER-ALZ2 study, treatment with donanemab was associated with a reduction in cognitive and functional decline from baseline to 76 weeks measured using iADRS compared with placebo with a statistically significant mean difference between groups of 2.92 in the mITT population.[6, 7]
- The key secondary outcome, CDR-SB, indicated a reduction in the rate of decline in the mean score at 76 weeks with donanemab compared with placebo, with a statistically

significant difference of -0.70 in the mITT population. Other secondary outcomes controlled for multiplicity including ADCS-iADL, ADAS-Cog_{13} and amyloid plaque deposition measured at 76 weeks indicated statistically significant differences between groups in favour of donanemab.[6, 7]

- In the indicated population (excluding ApoEε4 homozygous patients) the numerical mean difference between the donanemab and placebo groups at 76 weeks was 3.38 for iADRS and -0.77 for CDR-SB.[1]
- In the UK eligible population (excluding ApoEε4 homozygous patients and those on anticoagulants), the results are broadly consistent with the indicated population.[8]

4.2. Key uncertainties

- In the TRAILBLAZER-ALZ2 study, subgroup analyses based on ApoEε4 allele carrier status indicated that the beneficial effects of donanemab in iADRS and CDR-SB were less pronounced in patients with ApoEε4 homozygous status (17% [289/1736] of mITT population). This subgroup of patients were also observed to be at higher risk of developing ARIA adverse events. The MHRA concluded that the benefit did not outweigh the risk of treatment in ApoEε4 homozygotes and they were excluded from the UK marketing authorisation. The SPC also recommends that donanemab is not used concomitantly with anticoagulants because of the risk of ARIA-H and intracerebral haemorrhages. To reflect the patient population most likely to receive donanemab in practice, the submitting company provided evidence from a subgroup of patients that excluded ApoEε4 homozygotes and patients taking anticoagulants, described as the UK eligible population. Analyses in this subgroup was conducted post hoc and the study was not powered to detect differences between subgroups, therefore results are descriptive only.[6-8]

- The iADRS is a composite outcome of ADAS-Cog13 (measures cognition across 13 domains, scores range from 0 to 85) and ADCS-iADL (measures daily functionality across 23 items, scores range from 0 to 59), scores range from 0 to 144 with lower scores indicting greater disease severity. The between group difference in TRAILBLAZER-ALZ2 of approximately 3 points is modest for a scoring scale that ranges up to 144 points and the clinical relevance is uncertain. Furthermore, it is uncertain if a delay in disease progression of 1.4 months with donanemab would be clinically meaningful at this early stage in a chronic illness that can span years of a person's life. It is not possible to identify if a particular item or domain may have driven the iADRS score or how well correlated the component ADAS-Cog13 and ADCS-iADL scores were.[6, 12]

- The CDR-SB scale was a key secondary outcome used in the economic base case. This scale increases by increments of ≥ 0.5 points with progressive impairment. 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 six functional and cognitive domains, the individual benefit for patients will differ depending on which domain is more

affected in practice.[6, 13] In the supportive phase II TRAILBLAZER-ALZ study, there was no significant difference in CDR-SB between donanemab and placebo at 76 weeks.[11] This was a smaller study and excluded patients with high tau.

- The submitting company assumed that a >20% slowing of disease progression on iADRS and CDR-SB would demonstrate clinically meaningful benefit. It is uncertain if this threshold would correlate with a reduction in the decline of cognition and function that would have a meaningful impact on the quality of life of patients and their families. The QoL-AD scale measured HRQoL and did not show a significant difference between the donanemab and placebo groups at 76 weeks for the patients or caregivers. Clinical experts consulted by SMC indicated that as iADRS and CDR-SB scales are not widely used in the assessment of patients in practice it is difficult to know if a certain threshold would correspond to a clinically meaningful benefit, particularly due to heterogeneity in presentation and non-uniform pattern of progression.

- Blinding in TRAILBLAZER-ALZ2 could have been potentially compromised by the occurrence of infusion reactions, and ARIA adverse events. This could introduce bias for subjective outcomes if patients, caregivers or raters know study group assignment. To minimise this, risk raters for CDR-SB were blinded to adverse event information. Sensitivity analyses for iADRS and CDR-SB censoring change scores after the first observation of ARIA or infusion-related reactions were consistent in with the primary analysis and indicated benefit in favour of donanemab.[6]

- TRAILBLAZER-ALZ2 assessed the safety and efficacy of donanemab up to 18 months however controlled data beyond this are limited. Longer term effects are uncertain including maintenance of effect, amyloid reaccumulation and ARIAs.The submitting company provided indirect evidence that suggested a reduction in the CDR-SB was observed up to 36 months compared with data from the Alzheimers Disease Neuroimaging initiative real world evidence cohort but this was associated with limitations. The MHRA have requested that a post authorisation safety study is conducted to assess the incidence and severity of ARIAs, intracerebral haemorrhage and long-term safety. In addition, a controlled access programme will be implemented and will collect UK prescribing and adverse event data.[6, 7]

- The degree of cognitive impairment at screening was categorised based on MMSE score; a score of ≥27 defined MCI and a score of 20 to 26 defined mild Alzheimer's disease. Clinical experts indicated that although MMSE scoring is now less frequently used in practice, these scores and corresponding categories seem reasonable. In TRAILBLAZER-ALZ2, based on MMSE scoring at screening, 17% of patients in the donanemab group had mild cognitive impairment and 83% had mild dementia due to Alzheimer's disease.[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 addition, at baseline a substantial number of patients in the study (approximately 25% in the mITT population) had progressed to moderate Alzheimer's disease (MMSE score between 10 and 19) and

therefore initiated donanemab at a later stage of disease than specified in the marketing authorisation.[8, 14]

- In TRAILBLAZER-ALZ2, 61% of patients were receiving concomitant symptomatic treatment with an acetylcholinesterase inhibitor or memantine. In a sub-group analysis of iADRS and CDR-SB, the treatment effect favoured donanemab regardless of whether patients were taking symptomatic treatments at baseline. However the magnitude of benefit for iADRS appeared reduced for patients who were not taking symptomatic treatments at baseline (adjusted mean difference between groups 1.20).[6] This may affect the generalisability of study results to clinical practice, 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.

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

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 lack of long-term efficacy and safety data.

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 is required to confirm beta amyloid pathology. In addition, genetic testing of ApoEε4 phenotype to confirm heterozygous or non-carrier status is also 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, in order 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 significant 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 0.42% pharmaceutical company funding in the past two years, including from the submitting company. Alzheimer Scotland has received 0.34% 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 on what the company defined as the "UK eligible population". This was patients with MCI or mild AD dementia, who are ApoEε4 heterozygotes or non-carriers and who are not using an anticoagulant.
Comparators	Donanemab was considered as an add-on therapy to BSC. BSC was also the only included comparator. BSC consisted of pharmacological interventions and non-pharmacological interventions. Pharmacological interventions were AChEI 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 proportions adopted by the Expert Appraisal Group (EAG) within the NICE review of lecanemab, which were informed by clinical opinion. A six-month cycle length was used, with a half-cycle correction applied.[15]
Clinical data	The central source of clinical evidence was the TRAILBLAZER-ALZ2 study.[1, 6, 7] The treatment effect of donanemab 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 amyloids plaque levels would reach 24.1 CL. A waning period was assumed, with no treatment effect after 14.5 years post-treatment initiation, at which amyloids plaque levels would be around 50 CL. 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 AEs 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.[16] 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 was 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).[17] Utility values for patients in institutional settings were assumed the same as those in the community setting. Disutilities were applied for adverse events. Within their evidence, the submitting company has highlighted the significant carer burden that can result from AD. In response they looked to include carer health impacts in their base case. In line with standard SMC process these effects were removed from the base case but were explored in scenario analysis (See Section 6.3).
Costs and resource use	Medicine costs included in the model were diagnostic testing costs, acquisition costs, administration costs and AE 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. In the submitting company's base case health state resource costs were drawn from a source that included informal care costs. These fall outside of SMC's standard perspective. To better align with SMC guidance, an alternative source for health state resource costs were used, but results using the original source inclusive of informal care costs is presented as part of scenario analysis (See Section 6.3).
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. Inclusive of the PAS discount, the incremental cost effectiveness ratio was estimated as £18,892.

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 below. 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)
0	Base case	-	-	CiC	CiC	£18,892
1	Time horizon	28 years	20 years	CiC	CiC	£18,664
2	Starting population	38% MCI due to AD and 62% mild dementia due to AD	100% MCI due to AD	CiC	CiC	£9,189
3			100% mild dementia due to AD	CiC	CiC	£27,429
4			aligned to TRAILBLAZER-ALZ2: 21.2% MCI, 78.8% mild	CiC	CiC	£22,347
5	Treatment duration	Fixed duration (18 months) or treat-to-clear	Fixed duration of treatment only	CiC	CiC	£19,070
6			Treat-to-clear only	CiC	CiC	£16,513
7	Treatment effect	Hazard ratio estimated from TRAILBLAZER-ALZ2 study (HR considered CiC by submitting company)	Upper 95% confidence interval	CiC	CiC	£47,522
8			Lower 95% confidence interval	CiC	CiC	£8,331
9	Stopping rules	Treatment stops at movement to moderate or severe AD	Treatment stops at movement to severe AD	CiC		
10	Transition probabilities	NACC	Potashman et al (2021)	CiC	CiC	£17,940
11	Caregiver utilities	Excluded	Included	CiC	CiC	£10,724
12	Waning effect	Full treatment effect of donanemab is applied up to 5.5 years. A linear waning effect is	Increased duration of full treatment effect – up to 7.5 years	CiC	CiC	£17,541
13			Faster treatment waning – no	CiC	CiC	£19,905

		then applied with no treatment effect remaining at year 14.	treatment effect by year 12			
14			Faster treatment waning – no treatment effect by year 10	CiC	CiC	£21,204
15			Faster treatment waning – no treatment effect by year 8	CiC	CiC	£23,303
16	Health state resource costs	Wittenberg et al. (2019)[excludes informal care]	PSSRU (includes informal care costs)	CiC	CiC	£3,932
	Combined scenarios					
17	• Inclusion of carer disutilities (scenario 11) • Inclusion of carer costs (scenario 16)			CiC	CiC	£2,232
18	• 20 year time horizon (Scenario 1) • Patient mix matched to TARILBLAZER-ALZ2 (Scenario 4) • Fixed duration of treatment (Scenario 5)			CiC	CiC	£22,328

Abbreviations: AD: Alzheimer's disease; ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year; MCI: mild cognitive impairment; NACC: National Alzheimer's Coordinating Centre; PSSRU: Personal Social Services Research Unit; CiC: commercial in confidence

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 AD 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 model structure appeared appropriate and had good alignment with previous SMC submissions.

6.5. Key uncertainties

- State occupancy in the model was defined based on CDR-SB instrument. This was not the primary endpoint of the TRAILBLAZER-ALZ2 study, which was iADRS. The submitting company argued that the CDR-SB is commonly used in AD 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 associated with AD, 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 model assumed that of the patients starting donanemab, 38% would have MCI due to

AD, while 62% would have mild AD, aligned with the EAG preferred assumptions within the NICE appraisal of lecanemab. Given the complexities in diagnosing and initiating patients on donanemab, the starting proportions were seen as uncertain and subject to change over time, although the proportions adopted in the base case were informed by expert opinion. Further, the company did explore a number of scenarios assuming differing splits between MCI due to AD and mild AD groups (see Scenarios 2 to 4).

- There was some uncertainty over whether the slowed progression observed from donanemab treatment in the TRAILBLAZER-ALZ2 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 and the rate of return, with alternative assumptions explored (Scenarios 12 to 15). Given that donanemab led to large reductions in amyloid plaque levels alongside outcomes of uncertain clinical meaningfulness the inverse relationship between returning amyloid plaque levels and progression was also seen as uncertain.
- 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 estimated. The model used a 6-month cycle length to align with the clearance testing points of the TRAILBLAZER-ALZ2 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, and exploration by the SMC Assessment Team indicated that it may exaggerate the proportions of patients in the most severe health states. This could then exaggerate the estimated cost-effectiveness of donanemab by artificially inflating the incremental health benefits while deflating the incremental costs. The company noted that an alternative data source was explored in scenario analysis with minimal impact on the economic results (Scenario 10). However, this also used data from the NACC database and similarly estimated annual transition probabilities, so was not seen as suitably addressing the uncertainty.
- The company assumed that patients would stop when they transition to moderate or severe disease. Despite this rule being included 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 where patients would continue to receive treatment until they suffered severe AD (Scenario 9). The submitting company stated that given the stopping rule was stated in the SPC, it viewed that scenario as exploratory only and that the economic results are commercial in confidence and so cannot be reported here. An associated area of uncertainty was that treatment was assumed to continue when a patient was institutionalised, however the implications of that were expected to be small.

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

23 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.**	**44,158**

Costs from Dictionary of Medicines and Devices Browser on 02/02/25. 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 14 March 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.