Single Technology Appraisal

Donanemab for treating mild cognitive impairment or mild dementia caused by Alzheimer's disease [ID6222]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Donanemab for treating mild cognitive impairment or mild dementia caused by Alzheimer's disease [ID6222]

Contents:

The following documents are made available to stakeholders:

1. **Comments on the Draft Guidance 2 from Eli Lilly**

2. **Consultee and commentator comments on the Draft Guidance 2** from:
   a. Alzheimer's Research UK
   b. Alzheimer's Society
   c. Association of British Neurologists
   d. UK Clinical Pharmacy Association
   e. UCL Dementia Research Centre
   f. NHS England Infusion cost estimate

3. **Comments on the Draft Guidance 2 received through the NICE website**

4. **External Assessment Group critique of company comments on the Draft Guidance 2**

5. **Eli Lilly Managed Access proposal**

6. **NICE Managed Access Feasibility Assessment**

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

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Donanemab for treating mild cognitive impairment or mild dementia caused by Alzheimer's disease [ID6222]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on Thursday 27 March 2025. Please submit via NICE Docs.

Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly.

The Appraisal Committee is interested in receiving comments on the following:

- has all of the relevant evidence been taken into account?
- are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
- are the provisional recommendations sound and a suitable basis for guidance to the NHS?

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations:

- could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology;
- could have any adverse impact on people with a particular disability or disabilities.

Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.**

Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Eli Lilly & Company Ltd
Disclosure Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months. [Relevant companies are listed in the appraisal stakeholder list.] Please state: • the name of the company • the amount • the purpose of funding including whether it related to a product mentioned in the stakeholder list • whether it is ongoing or has ceased.	N/A

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Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	N/A
Name of commentator person completing form:	[redacted]

Comment number	Comments Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
1	**Executive summary** Lilly welcomes the opportunity to comment on the preliminary recommendation made by the appraisal committee detailed in the second draft guidance consultation document, following Appraisal Committee Meeting (ACM) 2, for donanemab in mild cognitive impairment (MCI) due to Alzheimer's disease (AD) and mild AD dementia. Whilst Lilly is disappointed that the committee's preliminary decision is to not recommend donanemab within its marketing authorisation, the company is committed to working with the National Institute for Health and Care Excellence (NICE) to address the external assessment group (EAG) and committee's key concerns, as outlined in the consultation document and the accompanying letter to company, to enable patients to access a disease-modifying treatment for the first time. **Updated patient access scheme** An updated patient access scheme (PAS) has been proposed for donanemab. The proposed donanemab price is [redacted] per vial, which is equivalent to an updated PAS discount of [redacted].

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	Revised base case results following DGD2 As part of the draft guidance response, Lilly have provided the results of the company revised base case following the second draft guidance document (DGD2), in Table 1. • The proportion of patients starting in the MCI and mild AD states has been changed to the values identified as the most plausible in UK clinical practice in the recent NICE committee appraisal of lecanemab, given the label patient populations are consistent (Comment 5)[1] • Unpaid care costs have been excluded from the model (Comment 7) • The hazard ratio (HR) versus best standard of care derived for disease progression as measured by the Clinical Dementia Rating – Sum of Boxes (CDR-SB) scale used in the model has been updated to the HR from the meta-analysis of TRAILBLAZER-ALZ 2 and TRAILBLAZER-ALZ on the UK eligible population ○ Lilly have chosen to adopt the committee's preference to move towards an agreed decision-making incremental cost-effectiveness ratio (ICER) • The source of the mortality risk between stages of AD has been changed, using Crowell et al. (2023),[2] in line with the EAG's base case ○ Lilly maintain that amyloid positivity plays a crucial role in determining mortality risk, alongside other limitations in the Crowell et al analysis including the cognitively normal reference group and their methodological approach to disease progression, as previously argued, however Lilly have chosen to adopt the committee's preference to move towards an agreed decision-making incremental cost-effectiveness ratio (ICER) The revised base case following DGD2 probabilistic cost-effectiveness results for donanemab versus established clinical management run with 1,000 iterations are presented in Table 1, and deterministic base case results are presented in Table 2. Donanemab was found to be cost-effective compared to best standard of care (BSC) at a willingness to pay (WTP) threshold of £20,000 per quality-adjusted life year (QALY), yielding an ICER of £27,831.

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Table 1: Summary of company revised probabilistic base case following DGD2 results (revised donanemab PAS price at DGD2 response)

Technologies	Direct costs (£)	Life expectancy (years)	Quality-adjusted life expectancy (QALYs)	Incremental costs (£)	Incremental life years	Incremental QALYs	ICER (£ per QALY gained)
Donanemab	[redacted]	[redacted]	[redacted]				
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£27,831

Abbreviations: BSC: best supportive care; DGD2: second draft guidance document; ICER: incremental cost-effectiveness ratio; PAS: patient access scheme; QALY: quality-adjusted life year.

Table 2: Summary of company revised deterministic base case following DGD2 results (revised donanemab PAS price at DGD2 response)

Technologies	Direct costs (£)	Life expectancy (years)	Quality-adjusted life expectancy (QALYs)	Incremental costs (£)	Incremental life years	Incremental QALYs	ICER (£ per QALY gained)
Donanemab	[redacted]	[redacted]	[redacted]				
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£27,366

Abbreviations: BSC: best supportive care; DGD2: second draft guidance document; ICER: incremental cost-effectiveness ratio; PAS: patient access scheme; QALY: quality-adjusted life year.

2

***De novo* long-term extension data**

Lilly acknowledges the concerns raised by the EAG and committee regarding the inherent uncertainties in the company's modelling of donanemab's long-term treatment effects, and as such, provide supplementary long-term extension (LTE) data to address this issue. The long-term extension study provides data to address uncertainties in treatment-effect estimates, assumptions regarding the long-term clinical effectiveness of donanemab and particularly the duration and waning of its effects after discontinuation.

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Data from the TRAILBLAZER-ALZ 2 LTE trial are now partially available, and as placebo patients in the trial were offered the opportunity to cross over to active treatment, no additional placebo data are available for comparison. [redacted] These data support and validate the long-term efficacy assumptions used within the company model. The methods and results of this analysis are described below.

Methods

[redacted]

[redacted] The National Institute on Aging and the Alzheimer's Association (NIA-AA) revised criteria for diagnosis and staging of Alzheimer's disease stated that CSF hybrid ratio [total-tau/Aβ42] is classified as a core 1 biomarker that is highly concordant with amyloid positivity on PET.[5]

[redacted]

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[redacted]

Results

[redacted]

Table 3: Demographic and baseline characteristics [redacted]

	TB2 Placebo	[redacted]	[redacted]

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	N=[redacted]*	N=[redacted]*	ESS=[redacted]
Age (mean (SD))	[redacted]	[redacted]	[redacted]
Gender, Male (%)	[redacted]	[redacted]	[redacted]
APOE4 Non-Carrier** (%)	[redacted]	[redacted]	[redacted]
MMSE (mean (SD))	[redacted]	[redacted]	[redacted]
ADAS-Cog$_{13}$ (mean (SD))	[redacted]	[redacted]	[redacted]
CDR-SB (mean (SD))	[redacted]	[redacted]	[redacted]

*for patients with non-missing displayed characteristics [redacted]
**Binary variable as homozygotes were excluded from the UK-eligible population.
Characteristics are displayed for the UK eligible population for TB2 and for the UK indicated population for [redacted].
Abbreviations: ADAS-Cog$_{13}$: 13-Item Alzheimer's Disease Assessment Scale – Cognitive Subscale; [redacted]; APOE4: apolipoprotein E ε4 (non-carrier vs heterozygote); CDR-SB: Clinical Dementia Rating – Sum of Boxes; ESS: effective sample size; Dona: donanemab; LTE; long-term extension; MMSE: Mini-Mental State Exam; N: Sample Size; SD: Standard Deviation.

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Figure 1: Standardised mean differences for baseline covariates [redacted]

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

Figure 2: [redacted]

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	[redacted] **Abbreviations**: [redacted]

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Figure 3: [redacted]

Abbreviations: [redacted]

Figure 4 shows a similar progression for the [redacted] and TRAILBLAZER-ALZ 2 placebo arm on the CDR-SB change from baseline up to Month 18, providing reassurance that the use of the [redacted] as an external control arm to represent placebo was reasonable.

Figure 4: TRAILBLAZER-ALZ 2 Placebo vs [redacted] up to 18 months

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Abbreviations: [redacted] CDR-SB: Clinical Dementia Rating – Sum of Boxes; CI: Confidence Interval; ESS: effective sample size; Dona: donanemab; LTE; long-term extension; MMRM: mixed model of repeated measures; N: Sample Size; TB2: TRAILBLAZER-ALZ 2; UK: United Kingdom.

Figure 5 shows the treatment effect of donanemab at Month 36 when assuming that the pattern of disease progression of the TRAILBLAZER-ALZ 2 placebo arm would be the same as for the [redacted]. This supports that the treatment effect of donanemab goes beyond the 18-month treatment duration, with the absolute difference between arms increasing between 18-months and 36-months.

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Figure 5: TRAILBLAZER-ALZ 2 LTE Donanemab vs [redacted] cohort up to 36 months

Abbreviations: [redacted] CDR-SB: Clinical Dementia Rating – Sum of Boxes; CI: Confidence Interval; ESS: effective sample size; Dona: donanemab; LTE; long-term extension; MMRM: mixed model of repeated measures; N: Sample Size; TB2: TRAILBLAZER-ALZ 2; UK: United Kingdom.

Sensitivity Analysis Results

To understand the long-term treatment effect in patients who had been off-treatment for the longest period, a sensitivity analysis was conducted in those patients who had cleared amyloid and discontinued treatment at 6-months in the double-blind phase of the TRAILBLAZER-ALZ 2 study.

Figure 6 shows the treatment effect of donanemab up to Month 36 for this population that cleared early. For this analysis, it appears reasonable for

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	the [redacted] to represent an external control of the TRAILBLAZER-ALZ 2 LTE. **Figure 6: TRAILBLAZER-ALZ 2 LTE Donanemab 6-month clearers vs [redacted] up to 36 months**  **Abbreviations**: [redacted] CDR-SB: Clinical Dementia Rating – Sum of Boxes; CI: Confidence Interval; ESS: effective sample size; Dona: donanemab; LTE; long-term extension; MMRM: mixed model of repeated measures; N: Sample Size; TB2: TRAILBLAZER-ALZ 2; UK: United Kingdom. All sensitivity analyses are presented in Table 4. [redacted]

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[redacted]

Table 4: TRAILBLAZER-ALZ 2 LTE Sensitivity Analysis Results

Analysis	Number of patients at baseline		[redacted]	[redacted]	[redacted]
	TB2	[redacted]			
Base Case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario: Entropy balancing	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario: GBM*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario: 6-month clearers	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario: 6-month clearers (Entropy balancing)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario: 6-month clearers (GBM)*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

Abbreviations: [redacted] CDR-SB: Clinical Dementia Rating – Sum of Boxes; ESS: effective sample size; GBM: generalised boosted models; LTE; long-term extension; TB2: TRAILBLAZER-ALZ 2.

Discussion

[redacted]

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	[redacted]. ***Limitation*** [redacted]
3	**Treatment waning assumptions** Lilly note that at the second committee meeting the EAG updated its waning assumption to assume a duration of five years. This was based upon their acceptance of evidence demonstrating that clinical progression and functional decline only occurred after four to five years in people with amyloid levels between 26 and 50 centiloids. However, Lilly would like to highlight that the EAG have not used the midpoint of this 26–50 CL range, instead selecting a threshold of 29 CL, this is detailed further below. ***Full treatment effect*** Following ACM2, the committee decided that *'the company's approach that assumed waning for 9 years and a total duration of donanemab effect (full and waned) of 14.5 years was implausible.'* Lilly reiterates that, as donanemab is an amyloid clearing agent, designed to remove amyloid in patients defined as 'amyloid positive', it is appropriate to assume retention of the full treatment effect of donanemab whilst patients remain 'amyloid negative', equating to an amyloid plaque level of <24.1 CL as used in TRAILBLAZER-ALZ 2. Notably, baseline amyloid levels in the TRAILBLAZER-ALZ 2 trial were ~100 CL. The threshold of 24.1 CL is a radiographic threshold of diagnostic, rather than clinical, relevance and equates to when the PET scan first reads positive, but is conservative, as higher thresholds of 30 CL have been used in comparable trials,[10] and literature suggests that amyloid has minimal clinical impact at this level.[11] Additionally, a threshold of 26 CL has been shown to effectively differentiate memory clinic patients who will progress to dementia from patients who will remain clinically stable six years after a PET scan, with higher thresholds showing

lower sensitivity.[12, 13]

The EAG however prefers to limit the duration of full treatment effect based upon the length of TRAILBLAZER-ALZ 2, which is arbitrary, with no bearing on the underlying pathophysiology. Lilly believes this to be overly conservative, as patients may still be classified as 'amyloid negative' at this level of burden in comparable trials and loss of full treatment effect runs contrary to the scientific evidence provided in the company responses.

Treatment waning effect

As highlighted at ACM2, the EAG's proposed waning has been revised based upon the evidence provided by Lilly from van der Kell et al. (2021),[14] but the threshold has been applied in a way that is not supported by this publication. The cited threshold of 26–50 CL has been used as a cut-off to indicate complete cessation of treatment effect, with five years of waning up until this point, when the literature supports waning to occur after this threshold. As acknowledged by the EAG, patients with an amyloid level of 26–50 CL would not be expected to experience any significant clinical progression for a further five years, making the EAG's assumption that all treatment effect is lost at 29 CL implausible. The EAG's approach is additionally conservative, as their modelling is based upon a threshold of 29 CL which is at the lower end of the 26–50 CL range and is a level that would still be considered 'amyloid negative', as highlighted by comparable trials that employed a stopping rule for amyloid negativity of 30 CL.[10] Even taking the midpoint of the range from van der Kell et al.[10] would equate to an additional three years of treatment effect, which is clearly significant to patients and their families.

Lilly reiterates that 50 CL is a more appropriate threshold for loss of treatment effect, due to the body of literature that indicates 50 CL to be the threshold for propagation of downstream tau, which is the primary mediator of amyloid-induced neurodegeneration and correlates directly with clinical and functional decline.[11, 13, 15, 16]

Amyloid-negative AD is a novel disease state with limited supportive literature specific to this unique population. Lilly has therefore been transparent about the necessity of utilising data from surrogate populations, whilst acknowledging the inherent limitations of doing so. Lilly strongly maintains that this is the most scientifically robust approach based upon the best data that are currently available.

The data from the TRAILBLAZER-ALZ 2 LTE presented in Response 2 addresses previous uncertainty around the rate of amyloid reaccumulation, demonstrating that a mean reaccumulation rate of [redacted] following treatment (derived from the updated exposure-amyloid plaque

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	model, including the *de novo* TRAILBLAZER-ALZ 2 LTE data and the TRAILBLAZER-ALZ 2 safety addendum data) is consistent with the initial model (2.8 CL/year) and demonstrates the modelled reaccumulation rate to be conservative, robustly validating Lilly's approach. Moreover, the observed increase in the amyloid plaque centiloid level in the UK-eligible population over 18-months during the TRAILBLAZER-ALZ 2 LTE period was [redacted], suggesting an approximate mean amyloid reaccumulation rate of [redacted], which suggests that the annual rate of 2.8 CL used to inform treatment-effect waning may lead to a conservative estimate of waning duration.
4	**Caregiver Utilities** As discussed during ACM2, it is important that the impact on caregivers is adequately reflected within the model. ***Psychometric properties of EQ-5D for caregiver utilities*** Lilly maintain that the EQ-5D is not an appropriate tool to assess health-related quality of life of caregivers for patients with AD. This is demonstrated both by the lack of face validity of the GERAS EQ-5D results and the ceiling effects that can be seen in Figure 7 below. A range of 37.0–38.6% of caregivers in the community setting reported to be in perfect health consistently across the disease states, which at face value does not appear to be plausible, especially within the severe health state, which reports the highest proportion of 'perfectly healthy' caregivers. The proportion of caregivers reporting perfect health and the consistency of the distribution of response scores across the disease states, suggest both a lack of responsiveness to different health states being assessed by the EQ-5D and a ceiling effect. As previously highlighted in the response to the first DGD, Reed et al (2017) suggests that the EQ-5D is not particularly effective at capturing the true impact on caregivers of caring for patients with AD dementia.[17] Examination of the EQ-5D domain scores showed that very few caregivers had extreme problems (<5% for any domain) and the levels of problems were generally similar at baseline and at 18 months, with more caregivers having some problems in the domains of pain/discomfort and anxiety/depression. As the GERAS study required caregivers to be the established caregiver, the impact on pain/discomfort and anxiety/depression scores may have been captured at baseline with low caregiver expectation of much change over time. These findings suggest that, because some of the EQ-5D domains are at ceiling scores (with few caregivers remaining in the study expected to decline much in the physical or emotional domains), caregiver EQ-5D is not a particularly informative or sensitive measure of the impact of caring for patients with AD dementia. It is possible that most caregivers who remained in the study were physically healthy and that patients discontinuing the study (for reasons including institutionalisation or death) were those experiencing more acute problems. The discontinuation of caregivers of these patients may thereby reduce the likelihood of observing caregivers with extreme problems.[17] The correlations between the EQ-5D and other measures like the Zarit Burden Interview (ZBI) and time spent on instrumental activities of daily living (T-IADL) were mostly weak or very weak. The paper surmises that the EQ-5D is not particularly

	effective for capturing the true impact on caregivers of caring for people with AD dementia as the EQ-5D index score had a low sensitivity to change over an 18-month period and was not clearly differentiated by patient AD dementia severity.[17] For the reasons presented above the EQ-5D values from the GERAS study do not appear to be suitable to inform the caregiver utility values used in the model.

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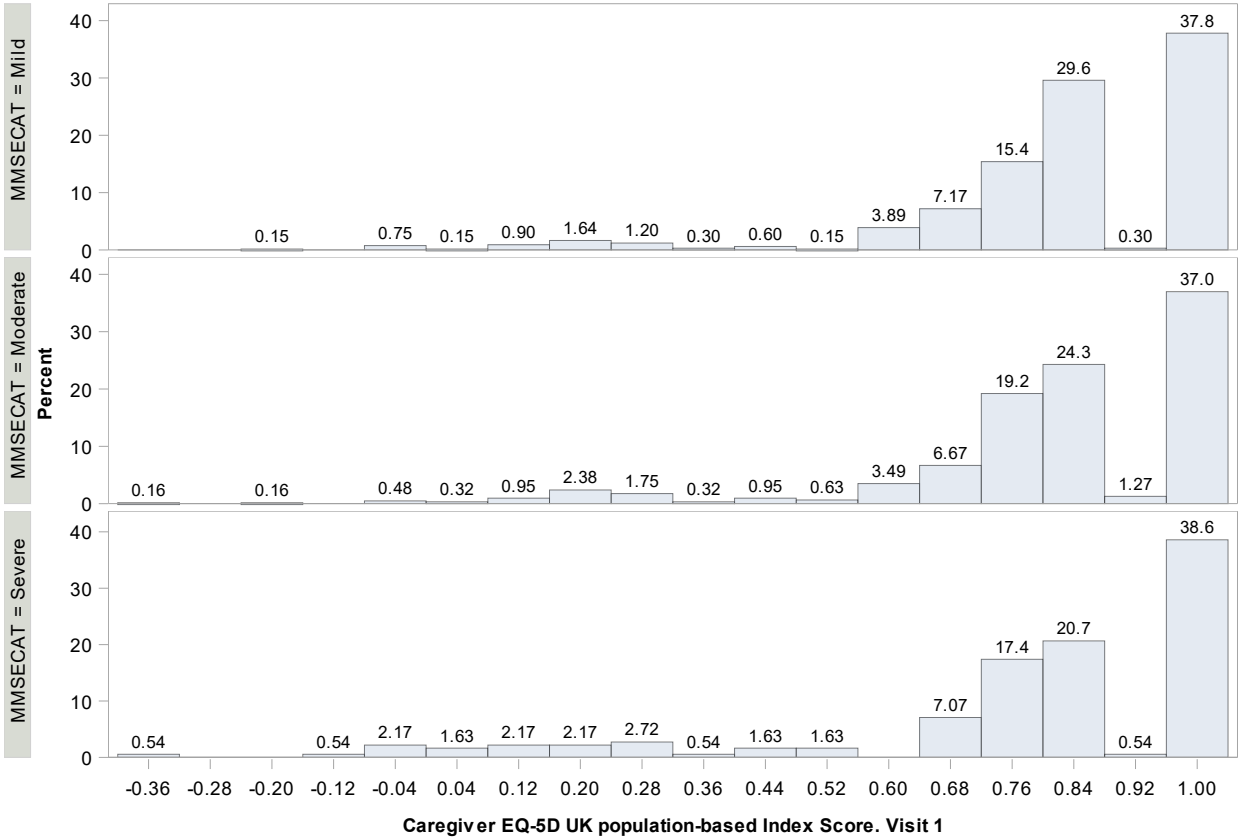
Figure 7: Caregiver EQ-5D UK utilities by AD severity from the Overall EU GERAS study



Abbreviations: AD: Alzheimer's disease; EQ-5D: EuroQoL 5-Dimentions; EU: European Union; MMSECAT: Mini-Mental State Exam category; UK: United Kingdom.

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	Caregiver Market Research Methods and Results Market research on caregivers was conducted to better understand both the emotional and task-specific burden of caring for a loved one with AD at different severity stages and how this burden evolves as the disease progresses. To accomplish this, a quali-quant survey was conducted through an online platform, where a group of caregivers provided individual, independent responses simultaneously to questions posed by a live moderator. While caregivers answered questions, integrated analysis features tallied the results in real-time which allowed for the capture of feedback from a larger group of caregivers in a shorter amount of time than traditional market research methods, such as phone conversations or surveys. The platform used open-end coding which assisted in the understanding of points of consensus and differences in the caregiver experience. Two sessions were conducted. The first session involved caregivers of patients in MCI or mild AD health states, and a second session involved caregivers of patients in moderate to severe AD health states. This approach allows us to examine how the caregiver burden changes over time as the disease progresses. Data from both groups of caregivers were used to assess the burden associated with the progression of the disease by asking key questions around caregiver tasks and what impact those tasks have on their QoL. Initial results from the market research showed that all caregivers experienced some degree of impact across all of the disease states, however responses differed between MCI / mild AD and moderate / severe AD groups, where a much greater burden was observed for the caregivers of moderate to severe AD patients, highlighting the increase in caregiver burden as the disease progresses. Key themes include increased burden as AD progresses and feelings of resignment and exhaustion manifesting over time for caregivers of patients with moderate to severe AD. Spontaneity is limited for caregivers of patients with MCI or mild AD, and is non-existent for caregivers of moderate / severe AD patients who often report a lack of autonomy or feelings of a loss of control over their life. This notably does not correspond with the shape of the results seen from the GERAS EQ-5D which, as previously stated, remained consistent across the disease states. As expected, caregivers for patients with MCI due to AD or mild AD have, on average, been providing care for their loved one for a much shorter period of time (Figure 8). Responses clearly suggested that providing care for a longer period of time was associated with feelings of being overwhelmed and exhaustion. **Figure 8: How long a caregiver has been providing care to their loved one**

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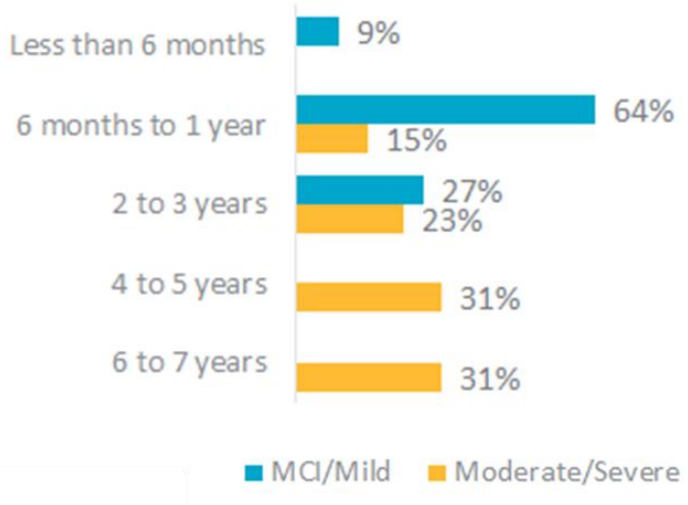

Abbreviations: MCI: mild cognitive impairment.

All of the moderate to severe AD carers spent at least three hours a day devoted to supervising or doing tasks for their loved one, with 67% spending 11 hours or more, suggesting round-the clock care. The full breakdown of responses to this question across the groups demonstrates the increasing burden as disease progresses. Qualitative responses also show that moderate to severe AD carers found that the burden of caring for their loved ones increased over time, with the following quotes: "*Her condition has gradually deteriorated over 5 years and the burdens increase daily*", "*It is 24 hrs care a day. Try to catch some sleep when possible*."

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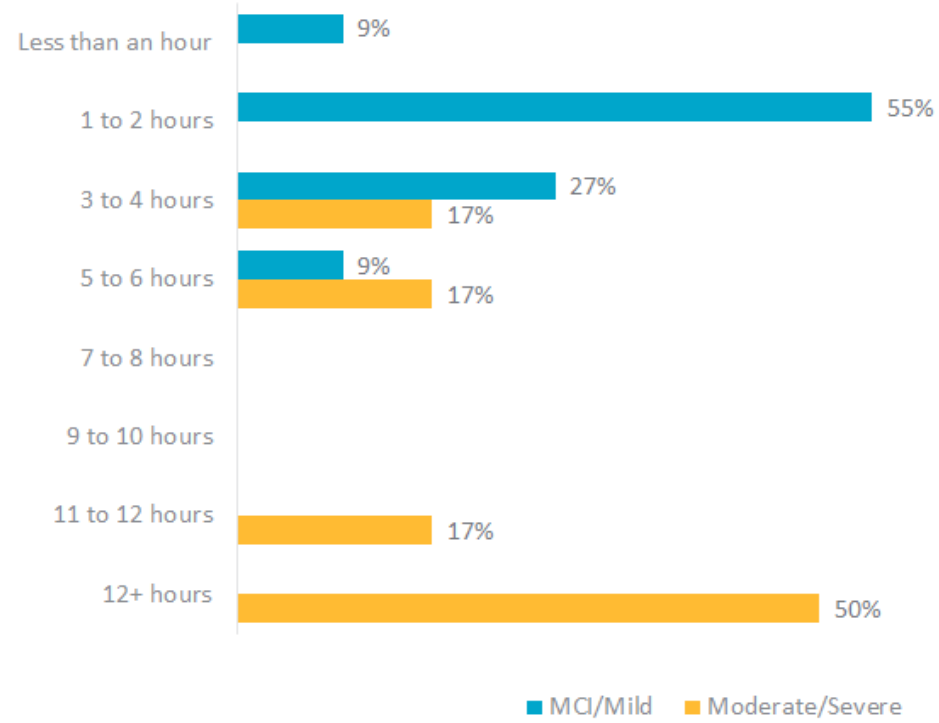
Figure 9: Time spent supervising or doing tasks in a typical day



Abbreviations: MCI: mild cognitive impairment.

A much higher proportion of caregivers for patients with moderate / severe AD reported experiencing a significant negative impact on their lives of providing care, while this value was 10% for caregivers of patients with MCI / mild AD. (Figure 10). Other responses included 25% of MCI / mild AD carers reporting a significant negative impact on their ability to make time for themselves, while 54% of moderate to severe AD carers reported significant negative impacts. Approximately 8% of MCI / mild AD carers reported a significant negative impact on their social life, and this figure rises

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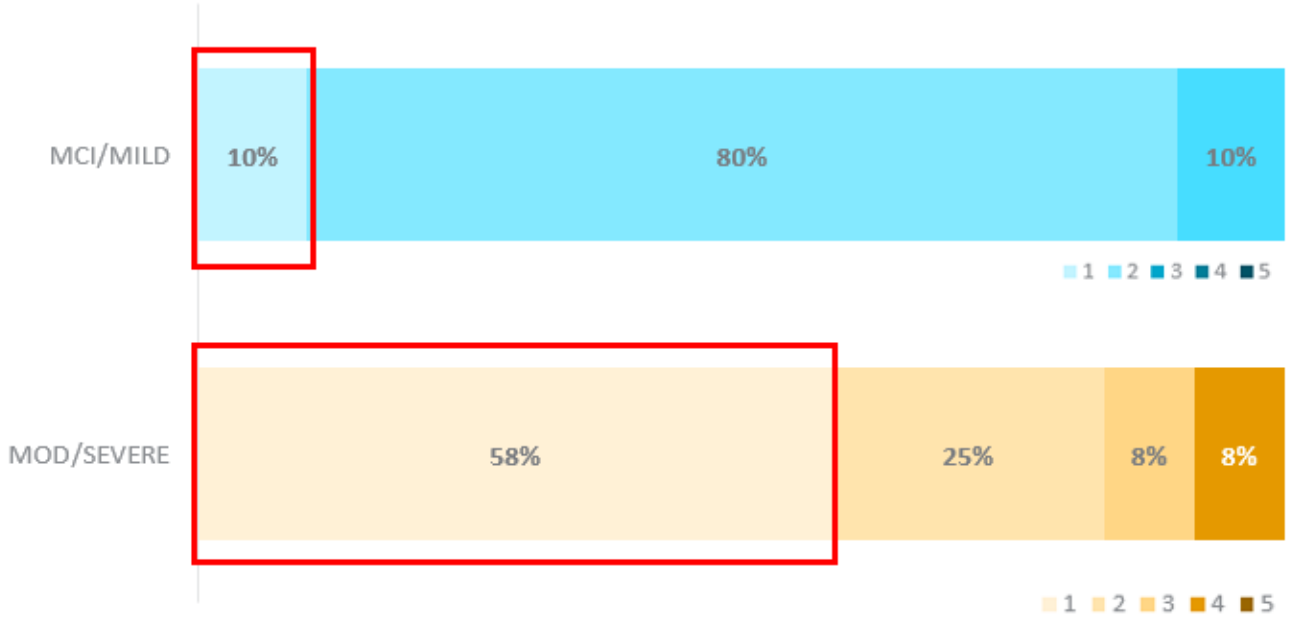
significantly to 57% of moderate to severe AD carers. Finally, 17% of carers of patient with MCI / mild AD reported a significant negative impact on their ability to control their life, rising to 57% for caregivers of patients with moderate / severe AD.

Figure 10: Impact of Caring for Loved One on Caregiver's Life



(1 = Significant negative impact, 5 = Significant positive impact)
Abbreviations: MCI: mild cognitive impairment; MOD: moderate Alzheimer's disease.

Carers of more severe AD patients also reported that they had to give up their freedom and social lives: "*I was independent before his diagnosis and had a lot of friends. I now have a handful of friends and haven't travelled anywhere in 5 years. Not one night away. I am looking for someone to care*

for him at nights.", "*Most of my social life is now none existent. I can't go out if I want to as she can't be left alone*".

Care for patients with moderate to severe AD can feel all-consuming: "*I have to do everything. He can only eat and brush his teeth*", "*He is my husband. I am on hand 24.7. I do everything. I manage the home, I manage our food shopping and all elements of cooking, I clean, I give him medication, ensure he is wearing clean clothes, I organise our entertainment. In short. I do everything.*"

These responses highlight a significant negative impact on the caregivers for moderate to severe AD patients in particular, which would be expected to be reflected in the utility values, which is not seen in the GERAS EQ-5D data.

Lilly will be able to provide the full market research report to NICE once it becomes available.

Alzheimer's Europe Caregiver Focus Group

Lilly commissioned a focus group of caregivers looking after people with AD which was shown both the vignettes preferred by Lilly and the EQ-5D instrument and asked to discuss how each option related to their personal experience of being a caregiver. The clear conclusion was that EQ-5D was not fit for purpose in capturing the longitudinal effect on caregivers, whereas the vignettes provided a much better representation of the caregiver journey. A transcript has been provided in the accompanying reference pack,[18, 19] but from this focus group Lilly would particularly highlight the following quotes from the focus group, and request that the Committee reconsider the caregiver perspective on this issue:

"But the utilities that you showed us from your study [i.e. from the vignettes] *are much more comprehensive and specific to the needs of people caring for people with dementia. This* [referring to the EQ-5D] *just isn't relevant as far as I'm concerned."*

"…it's that capturing of the stage that the person is at and you're showing the difference that happens to you as a caregiver during that progression. There's no way of capturing that from that blunt questionnaire."

"Because you know in the earliest stages, there was very little change in what I was able to do. And now as that has now progressed, it's made a significant difference. And I think that's what the vignettes capture – that progression through time as the illness progresses, moves on. The difference it makes to people is incredible." [Referring to how the definition of one's usual activities – one of the EQ-5D domains – changes through

	the caregiver journey, thus cause the EQ-5D to fail to capture the impact in later stages, as respondents refer to their current daily activities, not those they once were able to have] ***Scenario analyses*** For these reasons, Lilly maintain the base case approach previously presented, however recognise the uncertainty around the estimates of health-related quality of life (HRQoL) especially in the later stages of disease. Therefore, a key scenario analysis is presented using the EAG's scenario based on the company vignettes, presented in Table 5.

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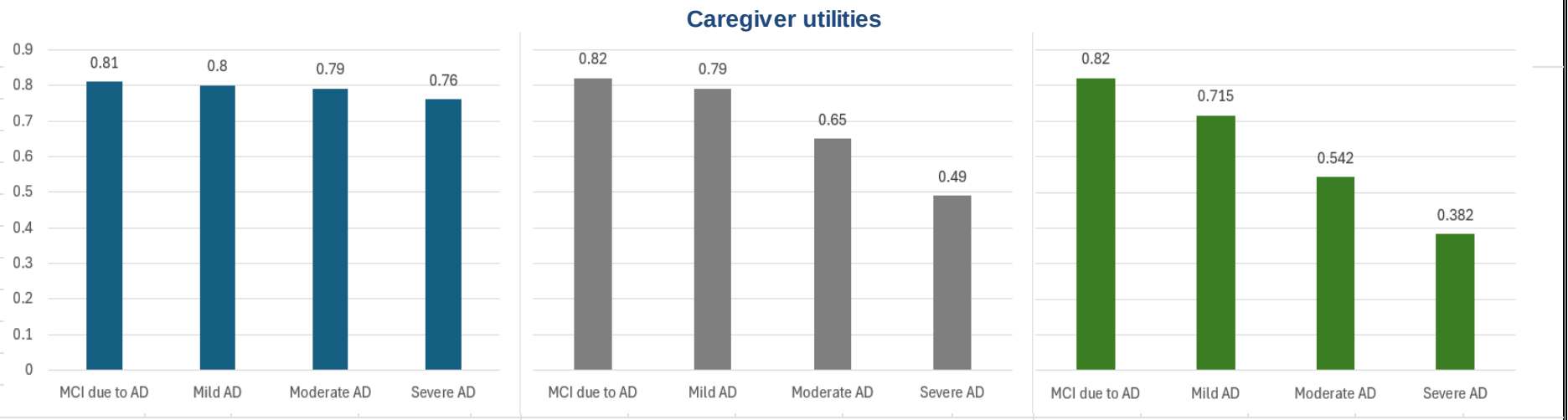
Figure 11: Comparison of Caregiver Utility Scenarios: Spouse Caregiver, Living in Community Setting



EAG (adjusted GERAS EQ-5D caregiver data)	EAG vignette studies (spouse/partner, community)	Company vignette studies (spouse/partner, community)

Abbreviations: AD: Alzheimer's Disease; EAG: External Assessment Group; MCI: mild cognitive impairment.

Note: GERAS values for moderate and severe disease were adjusted by the EAG to be below the general population utility value as the EQ-5D results (0.85 and 0.82, respectively) were above the general population utility norm for the people 68 years of age (general population norm = 0.8).[20] As previously noted by the company, the EAG's adjustment of the GERAS values to be below general population utility appears overly simplistic, as this results in a difference of only −0.04 to caregiver utility from mild to severe AD. Given the considered evidence presented above that highlights the impact of the disease on caregivers in detail, and how much this burden increases over time as the disease progresses, this simple reduction of the EQ-5D data appears to lack face validity.

Table 5: Scenario analyses (revised donanemab PAS price at DGD2 response) – caregiver utilities

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	Technologies / **Inc. costs (£)** / **Inc. QALYs** / **ICER (£/QALY)** Revised base case: Company vignettes as source of caregiver utilities / [redacted] / [redacted] / £27,366 Scenario: EAG vignettes as source of caregiver utilities / [redacted] / [redacted] / £29,888 Scenario: GERAS EQ-5D as source of caregiver utilities / [redacted] / [redacted] / £40,754 Scenario: Caregiver utilities not considered within the analysis / [redacted] / [redacted] / £43,197 **Abbreviations**: ICER: incremental cost-effectiveness ratio; Inc. incremental; PAS: patient access scheme; QALY: quality-adjusted life year.
5	**Proportion of patients starting in the MCI due to AD and mild AD dementia health states** Lilly recognise the committee's preference to use the proportion of patients in the MCI due to AD and mild AD dementia from the TRAILBLAZER ALZ 2 trial (20.4% in MCI due to AD and 79.6% in mild AD dementia) rather than the real-world evidence data published by Kile et al. 2024 (70% in the MCI due to AD and 30% in the mild AD dementia).[21] Lilly would briefly note that if this approach were to be taken, the figures should align with the UK-eligible population in the trial, which was 21.2% MCI and 78.8% mild AD. As described in the original company submission, differences in treatment effect were explored across the different AD severities. The Cox proportional hazard model described above defined clinical progression based on AD severity at screening (i.e. including only patients with MCI due to AD and patients with mild AD). The interaction between AD severity (at baseline) and the study treatment was tested and was found to not be statistically significant in the UK eligible population (p=[redacted]), with the same finding in the overall population (p=0.6286). The available evidence does not suggest that treatment effect would differ across the different AD severities; AD disease states are therefore not considered to be a treatment effect modifier. Therefore, the treatment effect estimated from the cox proportional hazard model should not be impacted by a distribution of MCI and mild AD patients that is different to the TRAILBLAZER-ALZ 2 UK-eligible population baseline severity split. In order to address the concerns of the committee, Lilly have updated their base case (Table 1) to use the proportions of patients starting in the MCI due to AD and mild AD dementia health states aligned to the values identified as most plausible proportions in UK clinical practice by an independent NICE committee in the appraisal of lecanemab (GID-TA11220), 38% in MCI due to AD and 62% in mild AD dementia.[1] However, given the stopping rule at moderate AD detailed in the donanemab marketing authorisation,[22] and notably the maximum duration of treatment for donanemab is 18 months compared to the continuous treatment of lecanemab,[22, 23] clinicians would be more likely to initiate treatment with donanemab at an earlier

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	stage of the disease and would be less likely to risk initiating in the later stages of mild AD. Therefore, Lilly consider that patients are more likely to initiate treatment in the MCI due to AD health state. As of 26th March 2025, the controlled access programme that is a condition of the donanemab MHRA license indicates that [redacted] of patients in the UK that have initiated on donanemab have MCI due to AD and [redacted] have mild dementia due to AD.[24] This is an early indication that biomarker confirmation and the availability of an effective treatment is likely to lead to earlier identification of patients and a higher proportion in MCI. Lilly's revised base case of 38% MCI can be viewed as conservative in light of this evidence. Additional data from the NACC and Swedish Dementia Registry (SveDEM) support this consideration by indicating that more patients are identified at the MCI due to AD health state when using biomarker confirmation. Of the incident sample identified within the NACC database who would be eligible for treatment with donanemab based on disease stage (MCI and Mild dementia due to AD), 41% had MCI due to AD and 59% had mild dementia due to AD. The SveDEM registry shows an increase in the proportion of patients identified at the MCI due to AD health state when using biomarker confirmation (34.5%) compared to clinical diagnosis alone (25.3%).[25] This reinforces that patients are more likely to initiate treatment with donanemab during the MCI due to AD health state, as upon the use of biomarker confirmation, more patients are identified in the earlier stages of the disease than identified by diagnosis alone. Furthermore, this demonstrates the impact of identifying patients based on biomarker testing in addition to standard clinical assessment in allowing AD patients to be identified at an earlier stage of disease. Both sources broadly support the proportion of patients used in the updated base case.
6	**Further information on the anticipated infusion cost associated with treatment with donanemab** Lilly acknowledge that there remains uncertainty surrounding the estimated infusion costs, with the company's preferred value (£207.59; 2021/22 reference costs: SB12Z) differing from the EAG's revised preference following ACM1, which aligns with NHS England's infusion administration cost estimate (£432; infusion cost for coronavirus monoclonal antibodies [COVID mAbs]). Lilly note a lack of transparency regarding how NHSE derived its cost estimate and how this relates to specific donanemab resource requirements.[26, 27] As stated in DGD2, *'the infusion cost for donanemab should reflect the health system resources required for giving an infusion of donanemab'.* As advised by NHSE, this is primarily dependent upon the complexity of drug preparation and administration, monitoring for IRRs and the complexity of the patient population. NHSE also advised against use of the simple parenteral chemotherapy infusion cost, stating '*donanemab is more complex to*

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	prepare, has the potential for more adverse reactions and people might have more complex needs', proposing the COVID mAbs costing as a more appropriate comparator. Lilly wish to provide data to address the inaccurate assumptions made by NHSE, and detail below why the proposed COVID mAb costing is an inappropriate comparator for this appraisal. ***Patient population*** • The infusion costs for COVID mAbs are reflective of a severely immunocompromised and medically complex patient population (for example those with HIV/AIDs or transplant recipients) who have an active, acute, and transmissible infection and who are, as defined by NICE, at the highest risk of hospitalisation and/or death[28] • In contrast, donanemab is a routine outpatient infusion for a chronic condition in a medically stable patient population. Lilly wish to emphasise that donanemab is only indicated for the very mildest stages of disease where there is minimal functional impairment, negating the need for additional resource requirements associated with more advanced stages of dementia • NHSE's assumption that cognitive assessment will be required during the infusion visit, is inaccurate and not supported by Lilly; further reducing NHSE's proposed resource requirements ***Drug preparation & administration*** • Donanemab is a simple, fixed-dose, monotherapy infusion which can be prepared on a ward and administered over at least 30 minutes (mean duration of 35.8 minutes)[29] of infusion time followed by 30 minutes of observation[29, 30] • Like donanemab, trastuzumab is a humanised IgG1 monoclonal antibody and was considered by NICE under the simple parenteral chemotherapy costing for metastatic HER2 positive gastric/gastro-oesophageal adenocarcinoma, as per advice from the NHSE Cancer Drugs Fund clinical lead. Trastuzumab however requires preparation in a laminar flow hood in the hospital pharmacy, weight-based dosing,

premedication and extensive monitoring, thereby potentially overestimating rather than underestimating the resource requirements for donanemab, as claimed[31]

Monitoring for IRRs

- Trastuzumab has a substantially higher rate of IRRs (40%) compared to donanemab (8.5%) and a higher risk of severe reactions associated with fatal outcomes,[31, 32] thus providing further support for the use of the HRG code SB12Z for donanemab's costing

Should the committee still perceive donanemab to be associated with greater infusion resource requirements, Lilly have provided the alternative option of the complex chemotherapy costing (utilising the SB13Z infusion cost of £256.95, taken from the 2021/2022 NHS Reference costs) in a scenario analysis (Table 6). However, this scenario remains inappropriate due to the simplicity of the donanemab infusion compared to the infusion process for more complex parenteral chemotherapy, which consists of 60 minutes nurse time and up to 120 minutes chair time for the delivery of a complete cycle.[33] Despite these additional considerations, the complex chemotherapy costing scenario is still substantially below that of the proposed mAb costing.

Table 6: Scenario analyses (revised donanemab PAS price at DGD2 response) – IV infusion cost

Technologies	Inc. costs (£)	Inc. QALYs	ICER (£/QALY)
Revised base case following DGD2: SB12Z Deliver of Simple Parenteral Chemotherapy (£207.59)	[redacted]	[redacted]	£27,366
Scenario: Neurology Consultant-Led (first attendance) Outpatient Attendance (Service Code 400 £222.91	[redacted]	[redacted]	£27,749
Scenario: SB13Z Deliver of Complex Parenteral Chemotherapy (SB13Z) £256.95	[redacted]	[redacted]	£28,600

Abbreviations: DGD2: second draft guidance document; ICER: incremental cost-effectiveness ratio; Inc: incremental; PAS: patient access scheme; QALY: quality adjusted life years.

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	10% COVID uplift in the infusion cost for coronavirus monoclonal antibodies (COVID mAbs) Furthermore, Lilly highlights an error in the infusion cost estimate derived by NHS England. The text in the previous response document regarding the derivation of the £432 IV infusion costs states, *"NHS England's pricing team estimate a resulting indicative local unit price, including Market Forces Factor (MFF) of £432. This is calculated by uplifting the £362 21/22 price using the annual inflationary % as published in the NHS Payment scheme".*[26] However, the original £362 tariff cited in the COVID MTA (TA878),[27] states, *"An indicative local tariff of £362 per spell plus Market Forces Factor (MFF) was suggested. This figure was based on national tariffs for similar treatments with a 10% COVID uplift".* The IV infusion costs for AD should be recalculated based on the original tariff prior to the 10% uplift. During the pandemic, special payment arrangements were implemented in the national tariff payment systems, however, as the COVID pandemic has subsided, the uplift is no longer applicable in this appraisal.
7	**Inclusion of unpaid care costs** Lilly continue to acknowledge the point raised by the EAG that the PSSRU report used to inform health care costs within the company model include unpaid care costs, which are not included within the NICE reference case.[34, 35] However, Lilly maintain its position for the consideration of care costs as a non-reference case scenario, notably, as invited by the NICE Lab report highlighted below.[36] Informal or unpaid care accounts for 40% of total dementia care costs and is estimated to total £18.2 billion in 2025,[37] with an estimated 1.1 billion hours spent annually on unpaid care for people with dementia.[6] A recent study found that informal care costs for dementia are significantly higher than in other disease areas, highlighting that direct health care costs account for only a minority of the overall costs of Alzheimer's disease (Figure 12).[38] This burden on families and society is often not fully captured in calculations of the costs of the disease,[7] and therefore, the consideration of unpaid care costs as a non-reference case scenario is crucial to highlight the significant burden of informal care in the UK and underscore the importance of broadening the cost-effectiveness analysis perspective.

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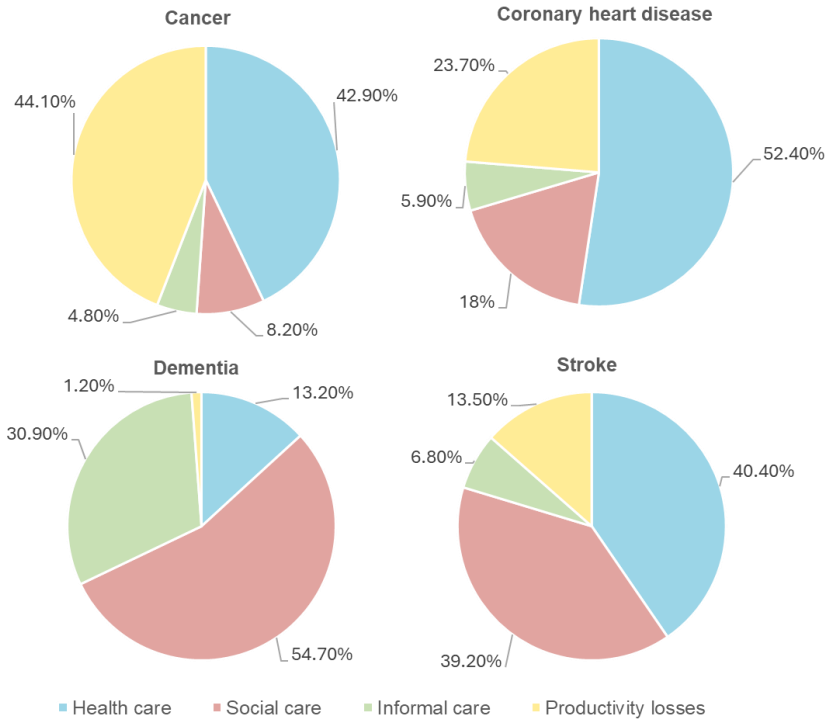
Figure 12: Distribution of total costs in patients with cancer, coronary heart disease, dementia and stroke in 2018



Source: Landeiro et al. 2024.[38]

The NICE HTA Lab report invites non-reference case analyses. On page 22, it states:[36]

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	"*As outlined in the section on economic evaluation in NICE's methods manual for health technology evaluations,*[39] *when care by family members, friends or a partner might have otherwise been provided by the NHS or PSS, it may be appropriate to consider the cost of the time of providing this care, even when adopting an NHS or PSS perspective. This can be presented as a non-reference case analysis.*" This suggests that even when adopting an NHS or PSS perspective, it is appropriate to consider the cost of care provided by carers. Therefore, while the base case has been updated to remove unpaid care costs, a non-reference case scenario analysis has been provided in Table 7. These results demonstrate that the inclusion of unpaid care costs has a significant impact on the cost-effectiveness results as the model input costs more accurately represent the share of informal unpaid care costs that were previously misclassified under health and social care. **Table 7: Scenario analyses (revised donanemab PAS price at DGD2 response) – unpaid care costs** **Technologies** / **Inc. costs (£)** / **Inc. QALYs** / **ICER (£/QALY)** Revised base case: Excluding unpaid care costs / [redacted] / [redacted] / £27,366 Including unpaid care costs / [redacted] / [redacted] / £21,082 **Abbreviations:** DGD2: second draft guidance document; ICER: incremental cost-effectiveness ratio; Inc: incremental; PAS: patient access scheme; QALY: quality adjusted life years.
8	**Updates to managed access agreement** Following feedback received from the second committee meeting, and within the DGD2, Lilly has revised the previous managed access proposal to provide additional information, addressing the key uncertainties identified by the committee. This will be provided to NICE as a separate document once available. The draft guidance document noted "significant concerns that implementation would lead to considerable burden with or without data collection in the NHS". This appears to refer to any burden on the NHS associated with setting up the service and pathways required to deliver amyloid-targeting therapies in clinical practice in the UK. Lilly is unclear as to the relevance of this point to whether donanemab may enter the IMF, as pathways must be established whether treatment is funded via managed access or in routine commissioning.

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	Lilly maintain that donanemab satisfies all criteria required to enter the IMF as it addresses a high unmet need, has potential to provide significant clinical benefits to patients, and represents a step-change in medicine for patients and clinicians.[40] Finally, Lilly has proposed a robust data collection framework which is targeted at the elements of uncertainty identified by the committee and the EAG which have the largest impact on cost-effectiveness estimates and will best inform future appraisal. • Long-term treatment effect • Baseline characteristics (including stage of disease at initiation) • Health care cost and resource utilisation

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- Do not include medical information about yourself or another person from which you or the person could be identified.
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- If you have received agreement from NICE to submit additional evidence with your comments on the draft guidance document, please submit these separately.

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NICE National Institute for Health and Care Excellence

Donanemab for treating mild cognitive impairment or mild dementia caused by Alzheimer's disease [ID6222]

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Alzheimer's Research UK

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Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	No links
Name of commentator person completing form:	[redacted]

Comment number	Comments Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
1	**Ongoing review of long-term data on donanemab is needed**. The company has extensive TRAILBLAZER study plans. We believe that as long-term study data becomes available, it will be valuable for NICE to incorporate these findings into their evaluation of donanemab's long-term efficacy.

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2	**We agree with the committee that there remains significant uncertainty surrounding infusion costs**. Notably, there is still a significant discrepancy between the company's cost estimate of £208 and NHS England's figure of £432 (previously £565). We would once again like to highlight estimates we obtained from clinicians regarding real-world infusion costs: 1. One clinician estimated the cost to be between £300 and £400 per hour of infusion. 2. Another clinician observed that £500 might be high but acknowledged it could reflect broader administrative and operational considerations. 3. A third clinician estimated that a 1-1.5-hour infusion would likely cost around £250 to £300, considering nurse time, overheads, and some clinician time. These estimates indicate that the real-world cost of infusion is uncertain and most likely lies somewhere between NHS England and company estimations. We believe **the committee should consider a managed access scheme** as this would allow uncertainties, such as infusion costs, to be clarified from real-world usage.
3	NICE, NHS England, and the company should **continue exploring the possibility of a managed access scheme** for donanemab. The innovative nature of donanemab means there are several uncertainties surrounding its real-world use. A managed access scheme would allow many of these questions to be answered as well as providing a range of benefits for dementia patients and the wider healthcare system. Managed access has the potential to: • Help determine the overall cost of treatment in a real-world NHS setting, including infusion costs. • Give a greater insight into the long-term efficacy of the treatments in a real-world population rather than a trial population. • Gain a greater understanding of the impact of lecanemab treatment on patient and carer quality of life, an aspect of the current evaluation which the committee notes there remains uncertainty. • Meaningful insights for research in Alzheimer's disease. • Help prepare the healthcare system for wider deployment of treatments in the pipeline. • Improve the lives of those affected by the disease. Concerns over barriers that exist to both implementation and data collection in the NHS should not prevent data collection efforts. While there may be challenges, including the lack of existing infrastructure or registries for Alzheimer's disease, these obstacles must be addressed proactively rather than delaying or halting real-world data collection altogether. Although we appreciate that resolving these issues is out of scope for a single technology appraisal, we believe that proactively addressing these obstacles through a managed access scheme will present a range of benefits. These include ensuring system readiness for future treatments in the pipeline and overall improvements in clinical care provided for dementia patients in the NHS.

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4	We feel **the true impact on carers' quality of life is not being incorporated** in the evaluation process. Although this aspect is mentioned in the guidance papers, the committee note there remains significant uncertainty around the impact on carer quality of life. We know the EQ-5D is generally used as a measure of quality of life in this area and we would like to understand the criteria NICE used to assess how appropriate a measure this is in reflecting the impact on carers for Alzheimer's disease patients.
5	Estimated at £21.1bn per year,[i] **the bulk of the cost of dementia care falls on unpaid carers** rather than in healthcare (£7.1 bn per year), and we feel that by not including the financial and productivity impact on carers of Alzheimer's patients in the evaluation, **the significant cost of informal care is being neglected**. While donanemab may not currently be deemed cost-effective due to other factors, considering informal care costs could have a substantial impact on the ICER. A thorough assessment of the treatment's value should consider that dementia costs are largely borne by individuals and families rather than the state. Given these factors, we would like to understand **if there is potential to apply a non-reference case to more accurately reflect these significant costs**. We also believe there would be **value in a managed access scheme** as this would allow the social and economic benefits that carers experience in a real-world setting to be captured. The committee would subsequently be able to make a more informed assessment on the economic impact unpaid care in the evaluation process.
6	We remain concerned that donanemab is not eligible for the severity modifier, despite Alzheimer's being the leading cause of death in the UK and imposing a significant disease burden. There is a clear clinical consensus that treating Alzheimer's in its milder stages is more beneficial than addressing it in later stages when care needs are much higher. However, donanemab is excluded from the severity modifier due to the age of the population and the chronic nature of the disease, which overlooks the condition's impact and the value of extending time in milder stages. We believe this approach needs reconsideration. We are aware of broader concerns about the severity modifier's role in limiting access to innovative treatments, as recently highlighted by the ABPI.[ii] [iii] We believe that the challenges posed by diseases like Alzheimer's should be considered, and the scope of the severity modifier should be expanded to better address such conditions in the future.

Insert extra rows as needed

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- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations.
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
- If you have received agreement from NICE to submit additional evidence with your comments on the draft guidance document, please submit these separately.

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Comments received during our consultations are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

[i] Alzheimer's Society and Carnall Farrar. The economic impact of dementia, Module 1, 2024. https://www.alzheimers.org.uk/sites/default/files/2024-05/the-annual-costs-of-dementia.pdf
[ii] Understanding medicines access: a look at the severity modifier and its impact (abpi.org.uk)
[iii] https://www.abpi.org.uk/media/rf1phcti/abpi-connie-2-report-august-2024.pdf

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Alzheimer's Society

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Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
Name of commentator person completing form:	[redacted]

Comment number	**Comments** Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
1	Alzheimer's Society welcomes NICE's appraisal of donanemab, the second disease-modifying treatment to be appraised by UK regulators, as an important milestone for dementia. We respect this second draft recommendation from NICE, whilst also recognising the disappointment that many people will have experienced on learning the decision. We accept NICE's assessment that the cost-effectiveness estimates for donanemab are uncertain but are above NICE's cost effectiveness threshold.

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2	We welcome NICE's decision to hold a second draft guidance consultation and a third committee discussion to consider additional data. We appreciate the rigour and flexibility demonstrated by NICE in their appraisals of the first disease-modifying treatments for Alzheimer's disease. We hope that learnings from this process will inform appraisals of future treatments.
3	We would also encourage NICE to monitor and review real-world data on the benefits and risks of donanemab, as well as data from any ongoing clinical trials.
4	We have no new evidence to submit further to our original evidence submission to the appraisal and our response to the consultation on the first draft guidance.
5	
6	

Insert extra rows as needed

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Association of British Neurologists

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Name of commentator person completing form:	[redacted]

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1	While differences in the cost-effectiveness modelling produced by the company and the evidence advisory group are expected, we note the extent of the discrepancy which is >10 times higher using the EAG calculations than those estimated by the company While some of the sources of these differences are redacted, factors influencing treatment-effect estimates include the proportions of individuals with MCI-AD and mild AD-dementia, how long benefits of treatment may last, health-related QoL of patients and carers, and infusion costs. These are addressed in turn below.
2	Proportions of patients with MCI-AD and mild AD We note that there is no exisiting NICE guidance on the diagnosis of management of MCI.The best real world data to indicate the likely proportion of MCI-AD versus mild-AD probably comes from the 2023 national audit of memory services : mas-2023-appendices-ii-v.pdf In this cohort of all patients seen in memory service, 17% were diagnosed with MCI, compared with 71% who had any type of dementia. (This is not specific to Alzheimer pathology but gives a useful indication of the ratio of MCI to mild dementia. 42% of cases of dementia were thought to be due to Alzheimer pathology. There is no estimate of what proportion of MCI is due to Alzheimer pathology but we might assume that this would be similar). In 2019, the figures were 17% for MCI and 67% for dementia, so there does not seem to be a trend for patients to present at an earlier stage over time. However, many neurologists believe that there will be a shift to earlier presentation as public awareness of potential disease modifying treatments grows.
3	Diagnostic costs Most neurologists believe that CSF biomarkers should be considered part of the “standard of care” in the diagnosis of dementia. However, we note that CSF biomarkers are only recommended by NICE if the diagnosis can’t be made using clinical assessment and brain scan (amyloid PET is not recommended) and that biomarkers are not routinely offered in memory services at present. . Although a blood test for AD pathology (p-tau217) is now available in an UKAS approved lab (https://www.uclh.nhs.uk/our-services/find-service/neurology-and-neurosurgery/neuroimmunology) it is not currently recommended by the manufacturer as a test for determining treatment eligibility. It may have potential to screen out individuals below the lower-cut point , but those with indeterminate or positive results would still need CSF examination or PET. It is unclear whether using blood biomarkers in the whole population to reduce CSF/PET use would be cost-saving overall. Further research on the real world use of blood based biomarkers in a UK memory clinic population would be useful. We agree that the cost of ApoE genotyping should be considered part of the cost of treatment.
4	Length of effect of treatment There are major differences in the assumptions about how long treatment effects will be sustained after treatment. We would welcome further evidence on this from longer term follow-up studies. It is biologically plausible that there could be a lag between amyloid re-accumulation and cognitive decline, as many experts believe that cognitive decline relates to downstream neurodegenerative effects of amyloid. It is possible that treatment effects will continue to *increase* (diverge from placebo) after treatment is stopped.
5	Health related QoL

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	We are concerned about the face validity of carer utility values which are virtually identical in MCI, mild AD, and moderate AD – as estimated using the adjusted GERAS EQ5D. By definition patients with MCI have normal activities of daily living, whereas those with dementia need assistance. Anyone living with dementia or caring for patients and caregivers with dementia will attest to the increased burden on carers as dementia starts and progresses
7	We continue to believe that a managed access programme within the NHS has the potential to provide invaluable information about implementation of these new therapies in a real-world setting, which is simply impossible in the (necessarily) artificial setting of a clinical trial. We consider that this is not impossible if carried out in selected specialist centres where the capabilities to safely deliver immunotherapies are already present. We would hope that a potential solution could be agreed between the committee and the company both to provide the required evidence on cost-effectiveness and long-term treatment benefit, and to help in the development of NHS pathways which need to be in place for this and other disease-modifying dementia treatments in the pipeline.

Insert extra rows as needed

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	UK Clinical Pharmacy Association (UKCPA) Neurosciences Committee

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Name of commentator person completing form:	[redacted]

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1	The Committee acknowledge the relatively moderate level of gains compared to risk and burden and contemplates whether investment might be more beneficial if directed toward improving pathways and care for all, rather than solely for eligible patients.

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2	The Committee reflected on the implication of genetic testing and feels the need of more clarification as well as care pathways that should include support for both patients and their families.
3	The Committee recognises the limitations of the population excluded from clinical trials (Down's syndrome, early onset dementia and some ethnic groups) but also acknowledge that clinical trials populations do not always reflect real-world diversity and lack of diversity in trials is a widespread issue across healthcare research.
4	The Committee recommends that the commissioning process should look at determining appropriate resource allocation across diagnosis, treatment, and cessation.
5	The Committee encourages real-world data collection through partnerships to allow pathway modifications if needed.
6	The Committee predicts a significant burden for the infusion unit (but recognised that is less than lecanemab) and many infusion units are already at full capacity hence they may struggle to support the treatment, as well as outpatient capacity.
7	The Committee acknowledge that additional training might be necessary for neurology, psychiatry, and geriatric medicine clinics.

Insert extra rows as needed

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- In line with the NICE Health Technology Evaluation Manual (sections 5.4.4 to 5.4.21), if a comment contains confidential information, it is the responsibility of the responder to provide two versions, one complete and one with the confidential information removed (to be published on NICE's website), together with a checklist of the confidential information. Please underline all confidential information, and separately highlight information that is submitted as 'confidential [CON]' in turquoise, and all information submitted as 'depersonalised data [DPD]' in pink. If confidential information is submitted, please submit a second version of your comments form with that information replaced with asterixis and highlighted in black.
- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations.
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments

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NICE National Institute for Health and Care Excellence

Donanemab for treating mild cognitive impairment or mild dementia caused by Alzheimer's disease [ID6222]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on Thursday 27 March 2025. Please submit via NICE Docs.

without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.

- If you have received agreement from NICE to submit additional evidence with your comments on the draft guidance document, please submit these separately.

Note: We reserve the right to summarise and edit comments received during consultations, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during our consultations are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

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	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.**
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Dementia Research Centre, UCL

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NICE National Institute for Health and Care Excellence

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Disclosure Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months. [Relevant companies are listed in the appraisal stakeholder list.] Please state: • the name of the company • the amount • the purpose of funding including whether it related to a product mentioned in the stakeholder list • whether it is ongoing or has ceased.	• I have served on advisory boards, provided consultancy services, or spoken at meetings for several pharmaceutical companies including Eisai and Lilly for which my employer UCL received payments. No payments from Eisai or Lilly to me personally. The focus was on clinical trials in Alzheimer's disease and included advice related to immunotherapies including those under consideration. • I am a member and former Chair of the Alzheimer's Society Research Strategy Council, which is my nominating organisation
Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
Name of commentator person completing form:	[redacted]

Comment number	**Comments** Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
1	**Model starting proportions - proportions of patients with MCI-AD and mild AD:** it is likely that awareness of possible disease-modifying treatments will lead to individuals coming forward earlier to seek advice about cognitive complaints. It is our experience in our Centre that individuals (and families) present later in the disease when they think there is little that can be done in terms of slowing progression. This is already changing and is likely to increase the proportion of people seeking advice at an MCI stage. The

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	availability of blood tests (plasma ptau217 is now available) could speed up the time needed to determine amyloid positivity and eligibility – this would also increase the proportion who are at an MCI-AD stage (vs mild AD stage) compared to estimates derived from current memory service surveys/data. A managed access scheme may well also use a fast track screening approach to reduce the time to diagnosis for those who might be eligible.
2	Utility values – carers: the EQ-5D scores derived from the GERAS study (Reed et al) appear very far from my experience as a clinician having discussed with many carers their concerns and distress and burden when caring for someone with dementia. Three of the 5 domains in the EQ-5D: mobility, self-care, and usual activities have little bearing on what the carers of my patients describe as the impact of caring. = I have discussed with carers how they feel their quality of life has been affected by their life partner / spouse having mild dementia or severe dementia – these are consistently much lower than the numbers presented at the meeting (derived from the Reed et al paper) 0.86 falling to 0.75. As a result, I conducted a questionnaire based (SLIDO) survey of attendees at the Alzheimer's Research UK Conference (March 2025) ~250 people responded (all answers were independently provided). I described what constituted a CDR score of 1 (mild dementia) and a CDR score of 3 (severe dementia). Participants were then asked a series of questions which included asking them to rate what they would estimate *their* quality of life to be if their partner/spouse (who they lived with) had MILD dementia – and then a similar question for *their* quality of life if their spouse/partner had SEVERE dementia - (on a 0 to 100 scale, where 100 is perfect health): Mean QoL rating for having a partner with **mild** dementia was 57.5 (or **0.58** on a 0-1 scale) (n=254) Mean QoL rating for a partner with **severe** dementia was 26.9 (or **0.27** on a 0-1 scale) These are unpublished results (manuscript in preparation) but they accord with my clinical experience of how much impact there is of caring for someone with severe dementia.
3	Carers: it is worth noting that most people that would be eligible start treatment would very likely have someone (partner/ care-giver) living with them – almost a pre-requisite for treatment – i.e. a minimum of one carer who will experience the impact of living with and caring for that perspm with dementia.
4	
5	
6	

Insert extra rows as needed

Checklist for submitting comments

- Use this comment form and submit it as a Word document (not a PDF).
- Complete the disclosure about funding from the company and links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into one response. We cannot accept more than one set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.

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- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations.
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
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Infusion Cost Estimates

Introduction

As part of the Health Technology Appraisals (HTAs) for donanemab and lecanemab, NHS England provided an estimate of the unit price for the administration of an infusion of a monoclonal antibody likely to be charged through the NHS Payment Scheme[1]. The NHS Payment Scheme defines the "rules to establish the amount payable for NHS-funded secondary healthcare."

NHS England is conscious that, as a material element of treatment costs, infusion pricing is an important consideration for the committee. Based on the supporting analysis summarised in this note, NHS England remains confident that its submitted estimate remains at the lower end of estimates of the price that would be paid by ICBs in a routine commissioning scenario.

Setting a price for monoclonal antibody infusion in Alzheimer's Disease or Dementia

As set out in previous notes, there is no Health Resource Group (HRG) code that covers a monoclonal antibody infusion to treat Alzheimer's Disease or Dementia currently in use. It is standard policy only to set a HRG price for a new area of activity up to three years after the activity starts in order for there to be sufficient reference data on which to base the price. Before then, it is normal to agree a price to be paid by commissioners (in this case ICBs) to NHS providers, using an estimate based on similar types of activity.

The methodology for estimating the average price for an infusion of a monoclonal antibody in the treatment of Alzheimer's disease, as submitted to NICE was as follows

Step 1	For each financial year (FY), define activity using
	• x292 Continuous intravenous infusion of therapeutic substance in combination with:
	  ○ x891 monoclonal antibodies band 1
	  ○ x892 monoclonal antibodies band 2

Step 2	Extract data from secondary user services dataset for • Admitted Patient Care (APC[2]) for both elective and day case • Outpatient attendance
Step 3	Remove non-elective zero price HRG activity (this where the system is used locally to record activity, but prices are not recorded accurately)

[1] NHS England » NHS Payment Scheme

[2] APC covers both elective admitted episode and day case. For the estimate both have been included due to inconsistent use of coding by NHS Providers. For elective episodes, spell has been limited to length of stay of zero or one to remove non-relevant episodes of care

Step 4	Limit Admitted Patient Care (APC) elective spells length of stay to zero or 1
Step 5	Calculate average price and uplift in line with NHS tariff inflation
Step 6	Apply average market forces factor (MFF)
	Point to note about NHS Payment Scheme: NHS tariff prices are used by commissioners to pay NHS providers for patient activity. This price covers the immediate cost of the appointment or procedure in terms of staff costs and consumables, plus an appropriate share of estates, patient transport costs, energy costs, training and other overhead costs. Medicine costs for the cost of monoclonal antibodies or other High Cost Drugs are explicitly excluded. It is therefore important, from a costing perspective, that other representations on price made to the committee consider the incorporation of equivalent elements.

The SQL code for this query can be found in the "SQL code" tab of the accompanying spreadsheet

The query estimate gives an average price of £361 from 227 episodes in financial year 2021/22. This is shown in table 1 below, along with, for completeness, values for other financial years.

Table 1: Output of price estimate query by financial year using codes x292 in combination with x891 or 892

Financial Year	Count	Total_Tariff_Initial_Amount	Average price
2018/19	320	155,427	486
2019/20	525	187,727	358
2020/21	63	23,139	367
2021/22	227	81,887	361
2022/23	195	75,546	387
2023/24	212	85,213	402

Adjusting the price to reflect advice from the pricing team that the resource for this type of infusion can be considered as similar to COVID MABs, and also in line with inflation, efficiencies, and an average Market Force Factor, gives a price estimate of £462[3].

[3] See "Inflation, efficiency, MFF" tab of accompanying spreadsheet for respective uplift factors

Re-running the estimate using data from 2023/24 gives a price estimate of £402 for 2023/24. Uplifting as above for inflation, efficiencies and average MFF gives a figure of £444. Applying the COVID resource factor would give a value of £489.

During the review of the price estimate, we noted that the volume of spells used to estimate the average price, at 227 in 2021/22, is low. Investigation showed this was a result of applying the restrictions to activity where the infusion of a monoclonal antibody had been explicitly specified in the SUS data (which is the coding approach we would recommend if routine adoption of either DMT is recommended by NICE). By removing the OPCS code restrictions of inclusion of either x891 or x892, the volume of activity increased to 530,402 in 2021/22. This is shown in table 2. Note removing this restriction, the price estimate increases to £535 at 2021/22 prices.

Table 2: Output of Price Estimate query by financial year using codes x292 only

Financial Year	Count	Total_Tariff_Initial_Amount	Average price
2018/19	268,750	142,726,726	531
2019/20	283,815	153,809,693	542
2020/21	422,207	223,568,212	530
2021/22	530,402	284,006,671	535
2022/23	586,570	320,180,539	546
2023/24	546,050	308,965,646	566

Applying the uplift factors for Covid, inflation, efficiencies and MFF gives a value of £589. Using more recent data for 2023/24 gives an unadjusted value of £566 and an adjusted figure of £688.

Table 3 shows the HRGs for which x292 code reports the most activity. For example, codes of FD02 and HD23 cover disease areas like Crohn's disease, colitis or rheumatology – areas known for the use of monoclonal antibody infusions.

Table 3 – HRG areas of activity by volume

HRG_Code	HRG_Name	Spell_Count
FD02H	Inflammatory Bowel Disease without Interventions, with CC Score 0	92,603
FD02G	Inflammatory Bowel Disease without Interventions, with CC Score 1-2	26,120
HD23J	Inflammatory, Spine, Joint or Connective Tissue Disorders, with CC Score 0-2	25,551
SA04L	Iron Deficiency Anaemia with CC Score 0-1	21,253
SA04K	Iron Deficiency Anaemia with CC Score 2-5	20,020
AA30F	Medical Care of Patients with Multiple Sclerosis, with CC Score 0-1	18,849
AB18Z	Continuous Infusion of Therapeutic Substance for Pain Management	14,247
AB18Z	Continuous Infusion of Therapeutic Substance for Pain Management	12,748

HD23H	Inflammatory, Spine, Joint or Connective Tissue Disorders, with CC Score 3-4	12,645
HD24G	Non-Inflammatory, Bone or Joint Disorders, with CC Score 2-4	11,164
WJ11Z	Other Disorders of Immunity	10,457
SA30D	Plasma Cell Disorders with CC Score 2-4	10,095
HD24H	Non-Inflammatory, Bone or Joint Disorders, with CC Score 0-1	9,749
SA04J	Iron Deficiency Anaemia with CC Score 6-9	9,189
HD23G	Inflammatory, Spine, Joint or Connective Tissue Disorders, with CC Score 5-6	7,343
PF27A	Paediatric Inflammatory Bowel Disease with CC Score 1+	6,610
SA30E	Plasma Cell Disorders with CC Score 0-1	6,292
AA30E	Medical Care of Patients with Multiple Sclerosis, with CC Score 2-4	6,213
JA12L	Malignant Breast Disorders without Interventions, with CC Score 0-1	6,207
PF27B	Paediatric Inflammatory Bowel Disease with CC Score 0	6,069
WH19Z	Potential Health Hazard Related to Communicable Diseases	5,254
HD24F	Non-Inflammatory, Bone or Joint Disorders, with CC Score 5-7	5,230
SA09K	Other Red Blood Cell Disorders with CC Score 2-5	5,068
AA30F	Medical Care of Patients with Multiple Sclerosis, with CC Score 0-1	4,807
SA30C	Plasma Cell Disorders with CC Score 5-7	4,745

Single Technology Appraisal

Donanemab for treating mild cognitive impairment or mild dementia caused by Alzheimer's disease [ID6222]

Comments on the draft guidance received through the NICE website

Name	[redacted]
Role	
Other role	
Organisation	Gloucestershire ICB
Location	
Conflict	No
Notes	

Comments on the DG:

- **Has all of the relevant evidence been taken into account?**

We cannot comment, although we note that there appear to be gaps in the current evidence for clinical and cost effectiveness.

- **Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?**

Yes. We agree that the summaries are an accurate interpretation of the evidence thus far.
We note that there appear to be gaps in the current evidence for clinical and cost effectiveness.
There remain concerns about the safety and efficacy of donanemab given the current evidence.
In addition, there is a lack of capacity and infrastructure in all local systems to ensure safe and equitable use of donanemab. Significant investment in local NHS services would be required to support safe and effective use.
We agree that insufficient benefits were demonstrated in clinical trials to justify a positive recommendation at this time.

- **Are the recommendations sound and a suitable basis for guidance to the NHS?**

Yes
We agree that insufficient benefits were demonstrated in clinical trials to justify a positive recommendation at this time.
If NICE approve for use in the future, it is vital that a suitable funding variation is put in place to ensure system readiness. NICE need to work with NHSE to ensure that an implementation plan and associated funding are agreed and in place before publishing a positive TA. This is needed to ensure patient expectations are managed, and that a consistent approach is

taken to implementing NICE guidance to avoid and variation in access to treatment and increasing health inequalities.
We have significant concerns about the high degree of uncertainties in both the clinical evidence and economic modelling and analysis. A negative recommendation needs to stay in place until these issues have been resolved.

- **Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?**

This would need to be considered as part of the funding variation.

Name	[redacted]
Role	
Other role	
Organisation	N/A
Location	
Conflict	No
Notes	
Comments on the DG:	

My comment as an individual is more of a plea. Please pass this drug on the NHS, it is a crucial turning point for Alzheimer's which has taken too long to arrive. It has been proven to clear amyloid plaque from the brain and cognitive decline hasn't happened as a result. What could be better than that? The cost will go down when it is on the NHS and at the same time it will save the NHS millions! In comparison I have a dear friend who is on a new cancer drug that she takes for 2 years after treatment at the cost of £50000 with no proof that it is successful. Come on NICE, donanemab is a miracle. I know I need it, I've just turned 60. Age shouldn't be a discrepancy when people have worked hard all their lives and then can't enjoy their later years and stripping their loved ones of them too. I have experienced it all. I have done drug trials, fund raisers. All I know is the NHS needs this drug.

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External Assessment Group Report commissioned by the NIHR Evidence Synthesis Programme on behalf of NICE

Donanemab for treating mild cognitive impairment or mild dementia caused by Alzheimer's disease [ID6222]: EAG's critique of the company's response to NICE Draft guidance: 2

Produced by	**Southampton Health Technology Assessments Centre (SHTAC)**
Authors	Keith Cooper, Principal Research Fellow, Health Economics Karen Pickett, Senior Research Fellow, Evidence Synthesis Joanna Picot, Senior Research Fellow, Evidence Synthesis
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Date completed	28th April 2025

[redacted]

TABLE OF CONTENTS

Acknowledgements

We thank David Alexander Scott, Principal Research Fellow, Statistics at SHTAC for providing advice to the project team.

LIST OF ABBREVIATIONS

ACM2	Appraisal Committee Meeting 2
AD	Alzheimer's disease
[redacted]	[redacted]
APOE 4	Apolipoprotein E4
BSC	Best supportive care
CDR-SB	Clinical Dementia Rating Sum of Boxes
CI	Confidence interval
CIC	Commercial in confidence
CL	Centiloids
CS	Company submission
CSF	Cerebrospinal fluid
DG1	Draft guidance: 1
DG2	Draft guidance: 2
EAG	External Assessment Group
ESS	Effective sample size
GLM	Generalised linear model
GBM	Generalised boost model
HRG	Healthcare Resource Group
HTA	Health Technology Assessment
ICER	Incremental cost-effectiveness ratio
LTE	Long-term extension
MCI	Mild cognitive impairment
MMRM	Mixed models for repeated measures
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
PAS	Patient access scheme
PET	Positron emission tomography
QALY	Quality-adjusted life year
RCT	Randomised controlled trial
SmPC	Summary of Product Characteristics
UK	United Kingdom

1 INTRODUCTION

This document is the External Assessment Group's (EAG's) critique of the response by the company, Eli Lily, to NICE's Draft Guidance: 2 document (issue date 27th February 2025) for the technology appraisal for donanemab for treating mild cognitive impairment or mild dementia caused by Alzheimer's disease [ID6222]. The EAG received the company's draft guidance response form, associated documents and revised model on 28th March 2025.

The company's draft guidance response contains the following documents:

- The draft guidance response form,
- Revised version of the company model

In this report we present the following:

- Our critique of the company's response to NICE's Draft Guidance: 2 document on donanemab for treating mild cognitive impairment (MCI) or mild dementia caused by Alzheimer's disease (AD) and the company's new evidence (Section 2)
- A validation of the results of the company's updated cost-effectiveness analysis (Section 3)
- The results of the EAG base case and scenario analyses (Section 4)

2 CRITIQUE OF THE COMPANY'S RESPONSE TO THE SECOND APPRAISAL CONSULTATION DOCUMENT

We have aligned our critique of the company's response to the draft guidance document with the numbered comments in the company's draft guidance response form.[1]

2.1 Comment 1: Executive summary

We have no comments to make regarding the company's executive summary of their response.

2.2 Comment 2: De novo long-term extension data

One of the substantial uncertainties listed in the Draft Guidance: 2 (DG2) document is how long the effects of donanemab last after stopping treatment. To help address this issue the company have provided data from the TRAILBLAZER-ALZ 2 long-term extension (LTE).

From information provided in the company's original submission (CS) we believe the TRAILBLAZER-ALZ 2 LTE has a duration of 78 weeks giving a total duration for TRAILBLAZER-ALZ 2 of 154 weeks (76 weeks double-blind period plus 78 weeks LTE), with amyloid plaque reduction measured at Visit 28 (Week 102) or Visit 35 (Week 130) (CS section B.2.3.2). At the end of the 76-week double-blind period of the TRAILBLAZER-ALZ 2 randomised controlled trial (RCT) placebo-treated participants were able to receive active treatment with donanemab in the open-label LTE period. Participants who had been randomised to receive donanemab during the double-blind period of TRAILBLAZER-ALZ 2 could:

- meet the treatment completion criteria (amyloid plaque level <11 Centiloids on any single positron emission tomography (PET) scan or ≥11 but <25 Centiloids on 2 consecutive PET scans) and receive placebo (this could have happened during the double-blind period or at the end of it)
- continue to receive donanemab in the LTE if they did not meet the treatment completion criteria at the end of the double-blind period.

The TRAILBLAZER-ALZ 2 LTE can therefore provide data for participants who met treatment completion criteria and stepped down from donanemab to receive placebo, thereby providing an indication of what happens to donanemab treated patients after stopping treatment. However, it cannot provide long-term data for placebo-treated participants because these people were able to receive active treatment in the LTE. The

company have therefore used an external control arm to represent placebo-treated participants.

2.2.1 External control for the TRAILBLAZER-ALZ 2 LTE

[redacted] The company state that they restricted the analysis to the UK eligible population of participants in the TRAILBLAZER-ALZ 2 LTE, which is appropriate. The company describe their [redacted] methods in comment number 2 of their response and these seem appropriate although [redacted] The EAG also notes that [redacted] The

demographic and baseline characteristics of the external control [redacted] in comparison to the TRAILBLAZER-ALZ 2 placebo arm (UK eligible population) are shown in Table 3 of the company response. [redacted].

2.2.2 Use of the external control

[redacted] The company describe their [redacted] method in comment number 2 of their response. Although this seems appropriate the EAG notes that [redacted]

[redacted] As Figure 4 of the company's response shows [redacted] The EAG agrees that this suggests that the use of the [redacted] external control arm [redacted] is reasonable.

[redacted] Although the company has not explicitly described this, we presume that the LTE data in Figure 5 for the donanemab arm includes participants who have completed their donanemab treatment and those who, because they did not meet the treatment completion criteria, were continuing to receive donanemab in the LTE. If this is the case, this does not align with what is expected to happen in clinical practice. The Summary of Product Characteristics (SmPC)[2] states that if monitoring for amyloid plaque clearance is not

possible, treatment should only be continued for a maximum of 18 months. If a patient progresses to moderate AD before the maximum 18-month treatment period, donanemab must be stopped. The impact of continuing donanemab use beyond the 18-month double-blind trial period and into the LTE on the adjusted mean change in CDR-SB is unknown. However there is a risk that in clinical practice the adjusted mean change in CDR-SB between months 18-36, when donanemab treatment has to be stopped after a maximum of 18 months, would be greater (i.e. more disease progression) than observed in the LTE. This is important because the company state that Figure 5 in their response "*supports that the treatment effect of donanemab goes beyond the 18-month treatment duration, with the absolute difference between arms increasing between 18-months and 36-months*". The analysis shown in Figure 5 of the company response reports a treatment difference between the donanemab arm and the external control [redacted] at 36 months of [redacted] for the adjusted mean change in CDR-SB.

2.2.3 Sensitivity analyses

The company base-case [redacted] method was the [redacted] but two other [redacted] methods [redacted] were used in sensitivity analyses with the results shown in Table 4 of the company response. The company also conducted a scenario analysis for the patients in the donanemab arm of the TRAILBLAZER-ALZ 2 trial, within the UK eligible population, who had cleared amyloid and met the treatment completion criteria to discontinue donanemab treatment at 6-months in the double-blind phase of the trial (n=[redacted]). The off-treatment follow-up period for these participants is therefore 30 months (12 months in the double-blind period of the trial plus 18 months of the LTE). The results of this scenario for the 6-month clearers are shown in Figure 6 and Table 4 of the company response. Figure 6 uses the [redacted]

[redacted]

[redacted]

The results of the sensitivity analyses in Table 4 of the company response show that the company's base case [redacted]

The results of the sensitivity analyses for the 6-month amyloid clearers [redacted]

2.2.4 EAG conclusion

[redacted] Our chief concerns are:

- [redacted]

- We believe that LTE data from participants from the donanemab arm in the double-blind phase of the TRAILBLAZER-ALZ 2 trial includes participants who have continued to receive donanemab in the LTE beyond the 18-month double-blind trial period. Therefore, this does not reflect the SmPC.[2] The use of donanemab between months 18-36 for some participants in the LTE creates uncertainty about whether the adjusted mean change in CDR-SB between months 18-36 observed in the LTE would have been the same if donanemab treatment had stopped for all participants after the initial 18 months of treatment in the double-blind phase of the trial.
- The sensitivity analysis for the 6-month clearers [redacted]

Despite the concerns above, the TRAILBLAZER-ALZ 2 LTE does provide additional useful data however we are more cautious in interpreting the findings than the company. This is because some participants continued to receive donanemab in the LTE beyond 18 months which may mean it is inappropriate to extrapolate treatment effects at 24 and 36 months directly from Figure 5 to clinical practice. The increase in the absolute difference between treatment arms between 18-months and 36-months, as shown in Figure 5, may be due to the continued donanemab treatment for some participants during this period for example. What would happen in UK clinical practice when donanemab would have to be stopped after a maximum of 18 months of treatment may not follow the same pattern. Similarly, although the sensitivity analysis for 6-month clearers provides evidence for a period of 30 months after stopping donanemab we again have a concern that these trial participants, who represent [redacted] of the relevant donanemab arm participants (n=[redacted]), might not be representative of the rest of the donanemab arm.

2.3 Comment 3: Treatment effect waning assumptions

At Appraisal Committee Meeting 2 (ACM2), the committee concluded that the company's approach that assumed waning for 9 years and a total duration of donanemab effect (full and waned) of 14.5 years was implausible. It concluded that based on the evidence presented it preferred the EAG's updated assumption for waning. It also concluded that this approach may be optimistic.

The company provided additional evidence on the long-term effect of donanemab on mean change in CDR-SB and this new evidence is discussed in this EAG critique in more detail in section 2.2.

The new evidence indicates that for those who have 18 months of treatment, the treatment effect appears to continue for a further 18 months (Company response Figure 5). However, as discussed in section 2.2 it may be inappropriate to extrapolate treatment effects at 24 and 36 months directly from company response Figure 5 to clinical practice. For those who discontinued treatment at six months (Company response Figure 6) the treatment effect appears to continue for a further 30 months, but as discussed in section 2.2 these participants may not be representative of all those eligible to receive donanemab. On the basis of this evidence, the EAG changes its base case and assumes that the treatment effect last for four years (1.5 years treatment and 2.5 years off treatment).

The company continue to assert that the treatment effect waning should continue for a further nine years after five years of full effect of donanemab. It also notes that in the EAG (and committee) assumption, the modelling is based on an amyloid threshold of 29 centiloids (CL), which is at the lower end of the 26-50 CL range and is at a level at which would still be considered 'amyloid negative' and therefore it is inconsistent that there is a loss of treatment effect at this level.

As advised by EAG's clinical advisers (and concluded in ACM2) the long-term effect of donanemab is uncertain and speculative and we note that the long-term effect is based on a surrogate outcome rather than the clinical outcome of progression of AD. Therefore, we have not changed our assumptions for the time-period of treatment effect waning (i.e. remains at 5 years).

2.4 Comment 4: Caregiver utilities

At the ACM 2, the committee concluded that they continued to prefer the GERAS study (Wimo et al. 2013 et al.[3]) for the caregiver utility values (EAG preferred source), as this was based on a large study giving UK relevant estimates and appeared reasonable. They also noted no new evidence had been presented at the ACM2.

The company continues to disagree with this source, as they consider it lacks face validity. They speculate that the study participants in the GERAS study may have only included caregivers who were physically healthy and that the patients who discontinued the study were those experiencing more acute problems. The company conducted market research on caregivers to better understand the emotional and task-specific burden of caring for a loved one with AD at different severity stages. Results from the market research showed the increased burden on caregivers, particularly those in more severe health states. Responses suggested that providing care for a longer time period was associated with feelings of being overwhelmed or exhausted. The company states that the responses indicate a significant

negative impact on the caregivers for more severe disease which would be expected to be reflected in the utility values, which is not seen in the GERAS EQ-5D data.

The company also commissioned a focus group of caregivers which gave their opinion on the vignettes preferred by Lilly and the EQ-5D instrument. The conclusion was that the EQ-5D was not fit for purpose and did not capture the longitudinal effect on caregivers whereas the vignettes provided a much better representation of the caregiver journey.

We acknowledge the significant burden on caregivers to patients with moderate and severe AD. However, as previously stated by the EAG, we note that most of the aspects that the caregivers of patients with AD reported to affect their daily quality of life are not directly related to health and therefore are not relevant for the health-related quality of life usually assessed within NICE appraisals. The exception is mental health. We note that EQ-5D has a dimension to capture the impact of the condition on mental health.

We have also previously reported the limitations of the company's vignette studies. We therefore consider that the GERAS study is the best available study for caregiver utilities for patients with AD.

2.5 Comment 5: Proportion of patients starting in the MCI and mild AD dementia health states

At the ACM 2, the committee concluded that they preferred the EAG's model starting proportions for the MCI and mild dementia caused by AD health states (20.4% in MCI due to AD and 79.6% in mild AD patients from the TRAILBLAZER ALZ2 trial).

The company disagree with the committee. They have updated their preferred proportions starting in the MCI and mild health states to that used in the NICE appraisal of lecanemab, i.e. 38% in MCI due to AD and 62% in mild AD patients, as these were considered the most plausible proportions for the UK in that appraisal. They consider that clinicians are more likely to initiate treatment at an earlier stage, as seen by the controlled access programme, where [redacted] started with MCI and [redacted] started with mild dementia due to AD. They also state that the available evidence does not suggest a treatment effect modifier and therefore the treatment effect estimated should not be impacted by a different distribution to that in the TRAILBLAZER ALZ2 trial.

Our preference for the EAG base case, as stated in our critique of the company response to the first draft guidance (DG1), is to maintain the alignment of the evidence source for the starting distribution of patients across MCI due to AD and mild AD dementia health states

and the source of effectiveness data, in order to maintain consistency with the clinical data used in the economic model. We note the small numbers in the controlled access programme ([redacted] patients) and question whether this is sufficiently large number to base any firm conclusions on.

2.6 Comment 6: Infusion costs for treatment with donanemab

At the ACM 2, the committee concluded that the cost of infusion remained uncertain and that it recommended using both the company and NHS England infusion cost estimates.

The company raise several limitations with the NHS England estimate of the infusion cost, such as the cost is for a medically complex patient population, whereas donanemab is a routine outpatient infusion for a chronic condition in a medically stable patient population and patients receiving donanemab have mild disease and minimal functional impairment. In addition, donanemab is simpler to administer than trastuzumab. On the basis of these limitations, they continue to assume that the infusion cost for donanemab would be £207.56.

The EAG assumed the same infusion cost for donanemab as the company in its base case in our External Assessment Report. We were not able to fully verify NHS England's proposed costs and preferred to apply them in a scenario than in our base case. We agree that if donanemab is recommended, the infusion costs would become clearer over time, as NHS England has indicated that a new Healthcare Resource Group (HRG) code will be created. Given the limitations raised by the company, which appear reasonable to the EAG, and the ongoing uncertainties in the infusion costs, we agree with the committee that the cost is likely between the company and NHS England estimates. We use the NHS England estimate in our base case and company estimate in a scenario analysis.

2.7 Comment 7: Inclusion of unpaid care costs

At the ACM2, the committee decided it was not appropriate for the company to include unpaid care costs in its model. It concluded that it preferred the EAG's approach of removing these.

The company acknowledged that unpaid care costs are not included within the NICE reference case and therefore have updated their base case to not include these unpaid care costs. However, they maintain their position that these care costs should be included as a non-reference case scenario, in order to highlight the significant burden of informal care in the UK, as outlined by the NICE Health Technology Assessment (HTA) lab report.[4]

The EAG welcomes the company changing their base case to exclude unpaid care costs, in line with the committee's recommendation. We have included this as a scenario, as requested by the company in 4.2.

2.8 Comment 8: Updates to managed access agreement

The EAG has no comments on the company's updates to the proposed managed access agreement.

3 VALIDATION OF THE COMPANY'S REVISED COST-EFFECTIVENESS RESULTS

3.1 Company's revised base case cost-effectiveness results

The company reports their revised base case incremental cost-effectiveness ratio (ICER) result in company response Table 2.

The cumulative effect of the changes implemented by the company, results in an ICER of £27,831 per quality-adjusted life year (QALY) (Table 1).

Table 1 Company revised model base case analysis with PAS

Treatment	Total costs	Total QALYs	Incr. costs	Incr. QALYs	ICER (£/QALY)
Donanemab	[redacted]	[redacted]	[redacted]	[redacted]	£27,366
BSC	[redacted]	[redacted]			

ICER, incremental cost-effectiveness ratio; PAS, patient access scheme; QALYs, quality-adjusted life years

The company have made the following changes since DG1:

- An updated patient access scheme (PAS) for donanemab of [redacted] per vial which is equivalent to a PAS discount of [redacted]
- The proportion of patients starting in the MCI and mild AD states has been changed to 38% MCI and 62% mild AD states (comment 5)
- Unpaid care costs have been excluded from the model (Comment 7)
- The hazard ratio versus standard of care is now taken from the meta-analysis of TRAILBLAZER-ALZ2 and TRAILBLAZER-ALZ
- The source of mortality risk between stages of AD has been changed to Crowell et al. (2023)
- Minor changes to the patients' utility values from the GERAS study.

The EAG reviewed the company's new model and agree that the changes listed have been implemented appropriately. With these changes, the EAG is able to replicate the changes made between the company's previous model (seen at Committee meeting 2) and their current revised base case.

4 EAG ANALYSES

4.1 EAG's preferred assumptions

Based on the EAG's critique of the company's model and the parameters and assumptions (discussed in section 2 and 3), we have identified several aspects of the company's revised base case with which we disagree. Our preferred model assumptions, which differ from the company's revised base case are:

- Apply waning of treatment effect from 8 cycles (4 years) for 10 cycles (5 years), (section 2.3).
- Carer utility values taken from GERAS study, as in the EAG original base case, with 1.8 caregivers (section 2.4).
- Proportion of patients starting in the MCI due to AD and mild AD dementia health states, as in the EAG and company original base case (20.4% MCI due to AD and 79.6% in mild AD dementia) (section 2.5).
- Infusion cost associated with treatment with donanemab of £432, as advised by NHS England (section 2.6).

The cumulative effect of the EAG's preferred model assumptions is shown in Table 2. The EAG's base case is £67,891 per QALY.

Table 2 Cumulative effect of the EAG's preferred model assumptions

Parameter		Treatment	Total costs	Total QALYs	Incr. costs	Incr. QALYs	ICER (£/QALY)
Company's revised base case		Donanemab	[redacted]	[redacted]	[redacted]	[redacted]	£27,366
		BSC	[redacted]	[redacted]			
1	Apply waning of treatment effect from 8 cycles (4 years) for 10 cycles (5 years)	Donanemab	[redacted]	[redacted]	[redacted]	[redacted]	£31,948
		BSC	[redacted]	[redacted]			
2	Carer utility values taken from GERAS study, as in the EAG original base case, with 1.8 caregivers	Donanemab	[redacted]	[redacted]	[redacted]	[redacted]	£48,898
		BSC	[redacted]	[redacted]			
3	Proportion of patients starting in the MCI due to AD and mild AD dementia health states, 20.4% MCI due to AD and 79.6% in mild AD dementia	Donanemab	[redacted]	[redacted]	[redacted]	[redacted]	£56,984
		BSC	[redacted]	[redacted]			
		Donanemab	[redacted]	[redacted]	[redacted]	[redacted]	£67,891

Parameter		Treatment	Total costs	Total QALYs	Incr. costs	Incr. QALYs	ICER (£/QALY)
4	Infusion cost associated with treatment with donanemab of £432, as advised by NHS England	BSC	[redacted]	[redacted]			
9	EAG revised base case	Donanemab	[redacted]	[redacted]	[redacted]	[redacted]	£67,891
		BSC	[redacted]	[redacted]			

AD, Alzheimer's Disease; BSC, best supportive care; EAG, External Assessment Group; ICER, incremental cost-effectiveness ratio; MCI, mild cognitive impairment; QALYs, quality-adjusted life years.

4.2 Scenario analysis conducted on the EAG's base case

The EAG conducted scenario analyses to evaluate the uncertainty around our assumptions in our base case (Table 3). The scenarios that have the greatest impact on the model results are using the caregiver utilities from the company vignettes which reduce the ICER to £43,621 per QALY.

The DG2 committee preferred assumptions gave an ICER of between £56,984 and £69,604 per QALY depending on the infusion cost used.

Table 3 Scenario analysis results, EAG's base case

Parameter		Treatment	Total costs	Total QALYs	Incr. costs	Incr. QALYs	ICER (£/QALY)
EAG revised base case		Donanemab	[redacted]	[redacted]	[redacted]	[redacted]	£67,891
		BSC	[redacted]	[redacted]			
1	Apply waning of treatment effect from 11 cycles (5.5 years) for 18 cycles (9 years)	Donanemab	[redacted]	[redacted]	[redacted]	[redacted]	£57,811
		BSC	[redacted]	[redacted]			
2	Include caregiver utilities from company vignettes	Donanemab	[redacted]	[redacted]	[redacted]	[redacted]	£43,621
		BSC	[redacted]	[redacted]			
3	Proportion of patients starting in the MCI due to AD and mild AD dementia health states, 38% MCI due to AD and 62% in mild AD dementia	Donanemab	[redacted]	[redacted]	[redacted]	[redacted]	£59,059
		BSC	[redacted]	[redacted]			
4	Infusion cost associated with treatment with donanemab of £208	Donanemab	[redacted]	[redacted]	[redacted]	[redacted]	£56,984
		BSC	[redacted]	[redacted]			
5	DG2 committee preferred assumptions with infusion cost of £208[a]	Donanemab	[redacted]	[redacted]	[redacted]	[redacted]	£69,604
		BSC	[redacted]	[redacted]			
		Donanemab	[redacted]	[redacted]	[redacted]	[redacted]	£83,011

Parameter		Treatment	Total costs	Total QALYs	Incr. costs	Incr. QALYs	ICER (£/QALY)
6	DG2 committee preferred assumptions with infusion cost of £432[a]	BSC	[redacted]	[redacted]			

AD, Alzheimer's Disease; BSC, best supportive care; DG2, draft guidance 2; EAG, External Assessment Group; ICER, incremental cost-effectiveness ratio; Incr., incremental; QALYs, quality-adjusted life years; MCI, mild cognitive impairment.
[a] DG2 committee preferred EAG base case with waning after 5 cycles (2.5 years) for 10 cycles (5 years).

5 EAG CONCLUSION

The company revised their base case following the second NICE draft guidance as discussed in section 2 and listed in section 3.1.

The EAG continues to disagree with some of the assumptions in the company's model. Our preferred assumptions include:

- Apply waning of treatment effect from 8 cycles (4 years) for 10 cycles (5 years), (section 2.3).
- Carer utility values taken from GERAS study, as in the EAG original base case, with 1.8 caregivers (section 2.4).
- Proportion of patients starting in the MCI due to AD and mild AD dementia health states, as in the EAG and company original base case (20.4% MCI due to AD and 79.6% in mild AD dementia) (section 2.5).
- Infusion cost associated with treatment with donanemab of £432, as advised by NHS England (section 2.6).

The company's base case ICER is £27,366 per QALY for donanemab versus best supportive care. Incorporating the EAG's preferred assumptions, the ICER increases to £67,891 per QALY. The model results are most sensitive to using the caregiver utilities from the company vignettes.

6 REFERENCES

1. Eli Lilly and Company. Donanemab for treating mild cognitive impairment or mild dementia caused by Alzheimer's disease [ID6222]. Draft guidance comments form., 2025.
2. Eli Lilly and Company. Donanemab Summary of Product Characteristics (SmPC), 2024.
3. Wimo A, Reed CC, Dodel R, et al. The GERAS study: a prospective observational study of costs and resource use in community dwellers with Alzheimer's disease in three European countries–study design and baseline findings. *Journal of Alzheimer's Disease* 2013;36(2):385-99.
4. National Institute for Health and Care Excellence (NICE). *Potential issues and challenges in evaluation of disease-modifying dementia treatments. HTA Innovation Laboratory Report. Available at: https://www.nice.org.uk/Media/Default/About/what-we-do/HTA%20Lab/HTA-lab-dmdt.pdf. [Accessed: March 2025]*.

B.1.1 *Managed access proposal*

Given the novel and innovative nature of donanemab, it may be a candidate for a recommendation through managed access. Lilly acknowledges that areas of uncertainty may remain in the cost-effectiveness analysis due to the limited long-term efficacy and safety data, uncertainty in healthcare cost and resource use, and uncertainty in terms of the cost-of-service expansion required to deliver amyloid-targeting therapies.

Further data are anticipated to become available during any managed access agreement timeframe, which should provide sufficient evidence for reducing uncertainty in those key areas. Ongoing studies are summarised by the key uncertainty that will be addressed in Table 1 below. Studies are categorized by the primary uncertainty that they are designed to address, though each study may also provide information on other uncertainties.

A full overview of studies included in the managed access proposal is shown in Table 2.

Additional Information Post-ACM2

During the second committee meeting and within the draft guidance document, the need for robust comparative data on the long-term effects of donanemab after treatment ends was clearly stated. Further information on the methodological approach is provided in Appendix A to provide the committee with reassurance that evidence generated will be robust.

It is also important to note that through a period of managed access data collection, two key uncertainties with large impacts on the economic analysis would be fully resolved.

- Comprehensive data will be available from the UK controlled access programme on the **proportion of patients initiating treatment within the MCI due to AD or Mild AD** stages of the model.

- Following the introduction of donanemab the treatment will be administered in the NHS. UK real-world evidence studies following the introduction of donanemab will provide information on the **IV infusion costs** and this uncertainty will be resolved.

Table 1: Planned studies: Summary by Primary Uncertainty

Study	Primary Endpoint Summary	Duration of Follow Up	Anticipated Availability
Primary Uncertainty: Long-term treatment effect			
TRAILBLAZER-ALZ2 EXT (Addendum 11)	Annualized mean change in amyloid plaque deposition following the last dose of donanemab as measured by florbetapir F 18 PET	Up to 48 months	[redacted]
TRAILBLAZER-ALZ5 (AACO)	Change from baseline through Week 76 in at least 1 of: - the overall population (combined population) or - the low-medium tau pathology population as measured by CDR-SB; ADAS-Cog13 score; ADCS-iADL score; MMSE score	18 months	[redacted]
TB-REAL-Global: Long-term comparative effectiveness study	Time to first increase in dependence level (SDS) (donanemab vs. usual care (i.e. non-ATT treatment)	5-years prospective	3-year data available ~2029
Prospective Evaluation of Early Alzheimer's in Real Life (PEARL)	Understand short-, medium-, and long-term real-world safety and effectiveness of treatment	5-years retrospective and 5-years prospective	[redacted]
International Registry for Alzheimer's Disease and other Dementias (InRAD)	A practice-based data collection and collaboration platform to support care and advance outcomes and epidemiological research in AD and other dementias. Minimum dataset domains: Global AD clinical staging, cognitive screening, functional scale and milestone events (change in living/work/driving status), safety assessments, brain imaging, treatments (Perneczky et al. 2024).	N/A	N/A
Primary Uncertainty: Healthcare Cost and Resource Use			
Alzheimer's Cost and HCRU Study	Current (BSC) HCRU and cost associated with AD by disease severity Predictors of high cost within AD	Retrospective UK Secure Data Environment Dataset	Q1 2025
Implementation of ATTs Cost and HCRU Study	Treatment-related HCRU and costs associated with initiation of ATT's HCRU and costs of patient monitoring during ATT treatment	Retrospective	Q1 2027

		UK Secure Data Environment Dataset	
UK Controlled Access Program	To register all patients prior to initiation of donanemab, promoting the safe and effective use of the donanemab	N/A	N/A
Additional Supplementary Data Collection Programs			
Post-Authorisation Safety Study (PASS)	Evaluate frequency of adverse events in donanemab treated patients, including ARIA-E/H, anaphylaxis and intracerebral haemorrhage >1cm	200 UK patients	[redacted]
Understanding donanemab target patient (EU)	To describe patient characteristics and clinical status in those receiving donanemab within the first year of launch	EU and UK countries in scope	Q1 2027
Real world effectiveness of donanemab (EU)	To assess treatment patterns and disease progression outcomes in donanemab treated patients	EU and UK countries in scope	Q2 2028
[redacted]	[redacted]	[redacted]	[redacted]

Table 2 provides a more detailed overview of planned and ongoing studies that would contribute to the reduction of uncertainty during the managed access period.

Planned and ongoing studies are categorized by the primary uncertainty that will be addressed; however individual studies may help to address several different issues. A full list of the uncertainties that we anticipate will be addressed by each study are listed in the right-hand column.

Table 2: Full overview of planned and ongoing studies and how they will address uncertainty in the model

Study	Primary Endpoint Summary	Key Secondary Endpoint	Duration of Follow Up	Anticipated Availability	UK Sites / Participants	Uncertainties Addressed
Primary Uncertainty: Long-term treatment effect						
TRAILBLAZER-ALZ2 EXT Addendum 11	Annualized mean change in amyloid plaque deposition following the last dose of donanemab as measured by florbetapir F 18 PET	[redacted]	Up to 48 months	[redacted]	Yes	Long-term clinical effectiveness (amyloid reaccumulation)
TRAILBLAZER-ALZ5 (AACO)	Assess rate of clinical progression (cognitive and/or functional decline) as measured by iADRS score in: - overall population and low-medium tau pathology at baseline	Change from baseline through **Week 76** in at least 1 of - the low-medium tau pathology population or - the overall population (combined population) as measured by CDR-SB; ADAS-Cog13 score; ADCS-iADL score; MMSE score	18 months	Q2 2028	Yes estimated 200 patients	Confirm clinical effectiveness and safety

		Change in brain amyloid deposition **Assess safety and tolerability of donanemab** **Evaluate the quality of life, dependency level, healthcare resource utilization,** as measured by QoL-AD, dependency level (derived from ADCS-ADL), RUD-Lite, and NPI				
TB-REAL-Global: Long-term comparative effectiveness study[1]	Time to first increase in dependence level (SDS) (donanemab vs. usual care (i.e. non-ATT treatment)	(i) Function (FAQ); (ii) Quality of Life (QoL-AD); (iii) Time to loss of Independence (SDS); (iv) Time to Institutionalization/Mortality; (v) Caregiver Burden (ZBI) (donanemab vs. usual care (i.e. non-ATT treatment)	5-years prospective	3-year data available ~2029	[redacted]	Long-term clinical effectiveness, quality of life, institutionalization and mortality, caregiver burden
Prospective Evaluation of Early Alzheimer's in Real Life (PEARL)[1]	Understand short-, medium-, and long-term real-world safety and effectiveness of treatment	Include diverse populations to understand their experiences with AD and treatment [redacted]	5-years retrospective and 5-years prospective	[redacted]	US data only [redacted]	Long-term clinical effectiveness Long-term safety Health care resource utilization

International Registry for Alzheimer's Disease and other Dementias InRAD	A practice-based data collection and collaboration platform to support care and advance outcomes and epidemiological research in AD and other dementias	Minimum dataset domains: global AD clinical staging, cognitive screening, functional scale and milestone events (change in living/work/driving status), safety assessments, brain imaging, treatments (Perneczky et al. 2024). [redacted]	N/A	N/A	International registry	Baseline Characteristics; Long-term clinical effectiveness; Long-term safety
Primary Uncertainty: Healthcare Cost and Resource Use						
Alzheimer's Cost and HCRU Study (UK)	Current (BSC) HCRU and cost associated with AD by disease severity Predictors of high cost within AD	Proportion of patients with MCI due to AD or mild AD dementia	Retrospective UK Secure Data Environment Dataset	Q2 2025	Not applicable	Cost and resource use in health and social care
Implementation of ATTs Cost and HCRU Study (UK)	Treatment-related HCRU and costs associated with initiation of ATT's HCRU and costs of patient monitoring during ATT treatment	Proportion of patients receiving PET imaging vs CSF (diagnostic) All-cause HCRU and costs Proportion of patients initiating donanemab with MCI due to AD or mild AD dementia	Retrospective UK Secure Data Environment Dataset	Q1 2027	Not applicable	Cost and resource use in health and social care
UK Controlled Access Program	To register all patients prior to initiation of donanemab, promoting the safe and effective use of the donanemab	Patient age, sex, APOE4 status, medical history, concomitant medications, AD stage at initiation, method of amyloid confirmation	N/A	N/A	All patients treated with donanemab	Baseline characteristics, Resource use of diagnostic approach
Additional Supplementary Data Collection Programs						
UK Post-Authorisation Safety Study (PASS)	Evaluate frequency of adverse events in donanemab treated patients, including ARIA-E/H, anaphylaxis and	Assess AE correlation with relevant risk factors Assess long-term safety events	~200 weeks, data collection terminates	[redacted]	200 UK patients	Baseline characteristics, long term safety information

	intracerebral haemorrhage >1cm		December 2030			
Understanding donanemab target patient (EU)	To describe patient characteristics and clinical status in those receiving donanemab within the first year of launch	Patient age, sex, medical history, concomitant medications, AD stage at initiation, donanemab dosing	Cross-sectional	Q1 2027	EU and UK countries in scope	Baseline characteristics of donanemab treated patients
Real world effectiveness of donanemab (EU)	To assess treatment patterns and disease progression outcomes in donanemab treated patients	Disease trajectories based on cognition and functioning; proportion of patients completing 18-month treatment, reasons for discontinuation	Up to 18m	Q2 2028	EU and UK countries in scope	Baseline characteristics of donanemab treated patients, clinical outcomes of treatment
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AD: Alzheimer's disease; ADAS-Cog$_{13}$: 13-Item Alzheimer's Disease Assessment Scale – Cognitive Subscale; ARIA: amyloid-related imaging abnormality; CDR-SB: Summary of Boxes of the Clinical Dementia Rating Scale; EXT: extension; iADRS: Integrated Alzheimer's Disease Rating Scale; MMSE: Mini-Mental State Exam; QoL-AD: quality of life: Alzheimer's Disease

[1] [redacted]

Appendix A - Additional Information Post-ACM2: Approach to long-term comparative effectiveness estimates

Although the use of observational study methods introduce additional risk of bias versus randomised controlled study estimates, methods are available and have previously been assessed by NICE which mitigate this risk as much as possible. As donanemab is licensed in the UK and the US as a safe and effective medicine, it is no longer ethical to perform randomisation especially over long-term study durations.

Methods to approach this challenge are available and have been used within previous NICE technology appraisals, particularly in oncology (examples can be found from TA677 and TA1042). Similar methods were also used to ensure balance in patient and disease characteristics between the placebo arm of the TB2 trial and the external control arm in the analysis of the TB2 long-term extension provided in response to the second draft guidance consultation on donanemab. Guidance on the use of such methods is available within the NICE decision support unit technical support documents 17 and 18.

To provide sufficient rigor for comparative analyses, both donanemab and usual care patients (i.e., patients without receipt of any amyloid-targeting agents) will be included in evidence generation efforts. [redacted]

This approach will enable faster and more efficient assessment of the benefits and risks of donanemab treatment in the real world.

Overview

Explanation

This page details the Managed Access Team's overall assessment on whether a medicine could be suitable for Managed Access and if data collection is feasible. The feasibility assessment does not provide any guidance on whether a medicine is a cost-effective, or plausibly cost-effective, use of NHS resources. This document should be read alongside other key documents, particularly the company's evidence submission and External Assessment Centre (EAC) report. Further detail for each consideration is available within the separate tabs.

Whilst a rationale is provided, in general the ratings for each area:
Green - No key issues identified
Amber - Either outstanding issues that the Managed Access team are working to resolve, or subjective judgements are required from committee / stakeholders (see key questions)
Red - The managed access team does not consider this topic suitable for a managed access recommendation.

The Managed Access Team may not assess other areas where its work has indicated that topic is not suitable for a managed access recommendation

The feasibility assessment indicates whether the Managed Access team have scheduled to update this document, primarily based on whether it is undertaking actions to explore outstanding issues. There may be other circumstance when an update is required, for example when the expected key uncertainties change or a managed access proposal is substantially amended. In these cases an updated feasibility assessment should be requested from the Managed Access team.

Topic name: **Donanemab for treating mild cognitive impairment or mild dementia caused by Alzheimer's disease**

Topic ID: **6222**
Managed Access Lead: **Steve Norton**
Date of assessment(s): **09/05/2025**

Is Managed Access appropriate - Overall rating	Comments / Rationale
Committee judgement required	There are some ongoing trials and observational studies which could generate further evidence. Data gathered via the company's proposed studies could provide some useful evidence to resolve the remaining uncertainties from ACM3. Longer term evidence will be available but the comparison will be between trial and observational data. The company's managed access proposal describes much of the nuance underpinning its strategy for mitigating bias in this comparison. Additionally, certain treatment waning scenarios cannot be tested within the time allowed for managed access. Quality of life data is being collected as trial and observational data but this uncertainty could also be resolved through clinical expert input. Health state occupancy at the start of the model could be resolved through managed access. This data would be from baseline only and therefore is likely to have high completeness. Infusion costs can be collected retrospectively but could also be resolved with expert input. The Committee is asked to consider the proposal in the context of the uncertainties, previously described implementation considerations, expected clinical benefits and whether or not a routine recommendation is possible.

Area	Rating	Comments / Rationale
Is the technology considered a potential candidate for managed access?	Yes	The treatment is in an area of high unmet need but it is not yet known if the ongoing trials will resolve committee's outstanding uncertainties.
Is it feasible to collect data that could sufficiently resolve key uncertainties?	Unclear	The company's proposal focusses on long-term treatment effect and healthcare cost and resource use as the main uncertainties. Data sources have been described that may provide useful additional evidence to resolve these uncertainties. The committee is required to determine if this data will allow them to make a firmer decision at managed access exit.
Can data collection be completed without undue burden on patients or the NHS system*	No	High burden on patients and the system to set up data collection as no RWE data collection is currently in place. This would be made more complex by needing to coordinate across primary and secondary care. A large indication with significant deviations from current practice risks high strain on the system.
Are there any other substantive issues (excluding price) that are a barrier to a MAA*	Yes - Major	Implementation would mean a large change to service provision and would need significant resource to roll out. Any restricted implementation would go against the IMF principles.

* Note NHS England is working on meeting the implementation challenges in this disease area, so there is scope for the RED ratings to change once implementation plans are known. It is acknowledged there will be further discussion needed with NHSE and the manufacturer if a provisional recommendation for MA is made.

Further managed access activity	Rating	Comments / Rationale
pre-committee feasibility assessment update		
pre-committee data collection working group		
pre-committee patient involvement meeting		

Key questions for committee if Managed Access is considered	
1	If managed access is recommended, does the whole proposal need to be implemented or can it be only one element, i.e. is the trial extension sufficient or will data from the SDE be required? Will additional data in clinical practice be required?
2	Data from the SDE would be site-specific. Does this make them unsuitable for future decision making for the whole NHSE population, or are they useful despite this?
3	For resource use data collected in clinical practice, would data need to be collected UK-wide, or would a small number of sites provide enough information?
4	If data from clinical practice are needed, would the burden be acceptable? Consider how much information these extra data will provide and whether this will aid decision making on exit.
5	The company proposes gathering baseline data on enrolment onto the technology. Is the committee satisfied that this will not represent a significant burden?
6	Will the ZBI assessment of caregiver burden and ADCS-ADL score for caregiver dependency be useful for decision making at managed access exit?
7	Does the committee believe the proposed data collection is sufficient to resolve its uncertainties after an MAA period? Is there sufficient value in entering an MAA as opposed to making a routine recommendation?

Early Identification for Managed Access

Explanation on criteria
These criteria should be met before a technology can be recommended into managed access through the CDF or IMF. To give a 'high' rating, the Managed Access Team should be satisfied that it can be argued that the technology meets the criteria. Companies interested in managed access must engage early with NICE and demonstrate that their technology is suitable for the managed access.

Date agreed with NHSE	10/05/2024

Is the technology a potential candidate for managed access?	
Rating	**Rationale**
Unclear	The treatment is in an area of high unmet need and the published data indicate some promise, but it is not yet known if the company's proposed methods of data collection will resolve committee's outstanding uncertainties.

IMF prioritisation criteria	Supporting Evidence
Potential to address a high unmet need	No effective treatment for Alzheimer's disease is available through the NHS. As a prevalent, degenerative disease, any treatment would be welcomed by patients and clinicians.
Potential to provide significant clinical benefits to patients	Early-stage evidence (pre-submission) showed some level of efficacy. The committee says the drug shows a small but clinically significant benefit.
Represents a step-change in medicine for patients and clinicians	An effective treatment for AD would be a step-change for patients and clinicians.
New evidence could be generated that is meaningful and would sufficiently reduce uncertainty	The clinical trial programme will continue to produce useful evidence for several years. It is not yet known if this will resolve committee's outstanding uncertainties.

System implementation	Supporting Evidence
The technology has been flagged as a potential IMF candidate to NICE by NHSE horizon scanning	This treatment is being considered as a candidate for a number of potential routes to commissioning.

Uncertainties

Explanation

This page details the Managed Access Team's assessment on whether data collection could sufficiently resolve key uncertainties through further data collection within managed access. The overall assessment is the key judgement from the Managed Access Team.

The Managed Access Team will justify it decision, but broadly it is a matter of judgement on whether the further data collection could lead to a positive NICE decision at the point the technology exits managed access. For this reason individual uncertainties that have a higher impact on the ICER have a greater impact on the overall rating.

Further detail is available on each uncertainty identified primarily informed from a company's managed access proposal, the External Assessment Group (EAG) report, judgements from the NICE Managed Access Team, and where available directly from NICE committee deliberations. The likelihood that data could sufficiently resolve each specific outcome is informed both by the expected primary data source in general (as detailed in the separate tab) and specifically whether the data collected is expected to sufficiently resolve that uncertainty.

Likelihood data collection could sufficiently resolve key uncertainties?	
Rating	**Rationale**
Medium	Most uncertainties below have been resolved through discussion at the committee meeting informed by clinical expert evidence and technical input. 4 remaining areas of uncertainty (listed as ACM3 1 to 4) could be reduced but not fully resolved through the proposed data collection in the company's managed access proposal - refer to the Trial Data tab. There is currently no long-term NHS-level data collection proposed. Longer term efficacy will be collected but will mean a comparison between trial and observational data - the committee needs to make a judgement on whether the potential value of longer term data outweighs the potential bias in this comparison. Data on caregiver utilities will be collected and could provide more evidence but quality of life (QoL) data collected as RWE is often incomplete and of low quality. Health state occupancy at the start of treatment will be collected through the NHS as proposed by the company - this does not carry the burden of continued data collection through follow-up and could provide useful information for decision making. Infusion costs could be collected through the healthcare resource usage study. NHSE have provided an updated breakdown of costs - the committee needs to decide whether further data collection is needed in light of this.

Key Uncertainties

Issue	Key uncertainty	Company preferred assumption	ERG preferred assumption	Impact on ICER	Data that could sufficiently resolve uncertainty	Proposed primary data source	Likelihood data collection could sufficiently resolve uncertainty	Rationale / Notes

ACM3; 1	Long-term treatment effect assumptions	(development from EAG7 and others)	(development from EAG7 and others)	High	TB-ALZ2 Addendum 11, TB-ALZ5, TB-REAL-Global, PEARL and InRAD are all stated as sources of data for reducing long-term effectiveness uncertainty. Comparison to be made between trial and observational data. Company aims to mitigate potential bias in the following ways: - Adjusting for patient and disease characteristics as per the examples in TA677 and TA1042 - Guidance from Decision Support Unit technical support documents 17 and 18 - Both donanemab and usual care patients (i.e., patients without receipt of any amyloid-targeting agents) will be included in evidence generation efforts	TB-ALZ2 Addendum 11, TB-ALZ5, TB-REAL-Global, PEARL, InRAD	Medium	The Committee must decide if the additional data available from the stated sources are sufficient and provide follow-up long enough to enable a routine commissioning recommendation after an MAA period. The TB-ALZ2 Addendum phase would provide an additional 48 months (max) of amyloid reaccumulation data, and TB-REAL-Global would contribute data at 3 and 5 years on other measures including QoL. The committee also needs to consider the appropriateness of comparing trial data with observational data. This comparison can bias the analyses in favour of donanemab. Committee should consider whether the mitigations proposed by the company will reduce the bias enough. Adjusting requires a rich dataset and careful inclusion of variables - committee need to indicate important variables in their decision making. Maximum time within managed access would not test the EAG's assumption of treatment waning. This would remain uncertain.
ACM3; 2	Caregiver utilities	(development from EAG9)	(development from EAG9)	High	The company's proposal features data that may resolve this uncertainty: TB-ALZ5 study and PEARL include measures of dependency. TB-REAL-Global is also proposed as a data source, gathering caregiver burden (ZBI) as its 5th named outcome.	Data collection in proposed studies; Clinical expert advice	Medium	Evidence to resolve this uncertainty is likely to come from clinical or patient expert advice to Committee. The company's proposed data collections may also contribute to resolving this uncertainty, though data quality and completeness for QoL measures from observational data can be poor. Committee needs to consider whether the ZBI and ADCS-ADL scores will be acceptable for decision making, compared with routinely accepted measures of QoL or more quantifiable outcomes.
ACM3; 3	Health state occupancy at start of model	(development from EAG8)	(development from EAG8)	High	Company's proposal UK Controlled Access Programme includes patient registration, including Patient age, sex, APOE4 status, medical history, concomitant medications, AD stage at initiation, method of amyloid confirmation. It is also feasible this could be adequately resolved at committee meeting by clinical expert opinion.	Data collection in clinical practice (UK CAP); Clinical expert advice	Medium	Subject to NHSE and company agreeing implementation of registration data collection, it appears feasible to gather data to resolve this uncertainty. Feasibility is stronger due to lack of a need to gather ongoing data - if the Committee requests long-term data collection in the NHS, this rating would reduce due to uncertainty over patient retention for data collection.
ACM3; 4	Infusion costs	£207.59 (SB12Z Deliver of Simple Parenteral Chemotherapy)	£432 (NHSE, based on COVID-19 monoclonal antibody infusion)	High	Healthcare resource costs	Implementation of ATTs Cost and HCRU Study	Medium	The study is retrospective which may not capture infusion costs accurately. Note: there is no clinical practice RWE data collection proposed in the company's current managed access proposal, though company-controlled data collection and data from UK SDE(s) are specified.

EAG1	Use of acetylcholinesterase inhibitors and memantine	The use of acetylcholinesterase inhibitors in people with MCI due to Alzheimer's disease and the use of memantine in people with either MCI or mild dementia due to Alzheimer's disease is outside the recommendations of NICE NG97. In the company's TRAILBLAZER-ALZ and TRAILBLAZER-ALZ 2 trials approximately 60% of participants received an acetylcholinesterase inhibitor or memantine	Although our clinical experts agreed that some people with MCI due to probable Alzheimer's disease would receive an acetylcholinesterase inhibitor off-label, neither of our experts stated that patients with MCI received memantine in clinical practice. We believe the use of acetylcholinesterase inhibitors and memantine in participants with MCI and the use of memantine for people with mild dementia due to Alzheimer's disease in the TRAILBLAZER-ALZ 2 RCT was higher than estimated in UK clinical practice	Unquantified	Additional data may become available from ongoing European and US studies into long-term effectiveness. EAG said: Additional discussion with clinical experts on the degree to which acetylcholinesterase inhibitors or memantine are used off label for people with MCI due to probable Alzheimer's disease and the degree to which memantine is used off label for people with mild dementia due to probable Alzheimer's disease in clinical practice. Discussion about the potential impact of acetylcholinesterase inhibitors or memantine on measures of cognition and function in people with MCI or mild dementia due to probable Alzheimer's disease.	Clinical expert evidence; further data collection	No further data collection possible / proposed	It is plausible that data collection in clinical practice could produce a more generalisable population in terms of level of acetylcholinesterase inhibitor use, however this has not been proposed. It is not clear that acetylcholinesterase inhibitor effect would be significant, therefore the value in collecting these data are also unclear. The clinical trials and pragmatic RWE studies are not powered to generate estimates of treatment effect within the subgroup of patients who are on / off concomitant treatments. As described in the NICE submission documents, the proportion of patients on concomitant medications was balanced across arms in the TB2 trial. However if this is flagged as an uncertainty within the managed access feasibility assessment, the results of TB-5 (with sites in the UK) may provide a future source of additional evidence that is more generalizable to NHS practice in terms of concomitant symptomatic treatment use
EAG2	Choice of measure of cognition and function for use as the outcome measure of treatment effect in the economic model	EMA guidance published in 2018 on the clinical investigation of medicines for treating Alzheimer's disease states that there is no ideal tool for assessing the efficacy of treatments for dementia and considers a range of tools may be needed to assess treatment efficacy in a trial.	The company's TRAILBLAZER-ALZ and TRAILBLAZER-ALZ 2 trials used five different measures (iADRS, CDR-SB, ADCS-iADL, ADAS Cog13 and MMSE) to measure cognition and/or function (disease progression). The iADRS was the primary outcome of both trials but CDR-SB from the TRAILBLAZER-ALZ 2 trial has been used as the measure of treatment effect in the economic model. On balance, we feel the use of the CDR-SB measure to inform the treatment effect in the company's economic model is appropriate, but we acknowledge that there is value in considering the iADRS as an alternative.	High	EAG said: We requested (clarification question B5c) that the company provide the hazard ratio of progressing to clinically worse health states between donanemab and best supportive care for the iADRS measure and enable its use in the model	Clinical expert evidence	No further data collection possible / proposed	Resolution of this uncertainty does not lend itself to further data collection, due to this being a methodological choice.

EAG3	Analysis of clinical effectiveness results for use in the economic model	The company use a hazard ratio of disease progression (0.62, 95% CI 0.52 to 0.75) based on the CDR-SB outcome as a measure of treatment effect in the economic model that is estimated from the phase 3 TRAILBLAZER-ALZ 2 RCT only. In response to clarification question B5c the company have also provided a hazard ratio of disease progression based on the iADRS outcome from the TRAILBLAZER-ALZ 2 RCT (0.70, 95% CI 0.58 to 0.84). In the phase 2 TRAILBLAZER-ALZ trial the CDR-SB least squares mean change difference between the trial arms was smaller than for the TRAILBLAZER-ALZ 2 trial whereas the least squares mean difference in iADRS score was larger than for the TRAILBLAZER-ALZ 2 trial	The reasons for these differences are not easily explained. They could be a consequence of the slight differences in methodology of the trials and the differences in participant characteristics or they may be a consequence of the variability in the disease course between patients. We believe that, as the patients in both trials are representative of the patients who would receive donanemab in clinical practice, there should be the option to use data from both trials combined in the economic model.	Unquantified	EAG said: We asked the company to conduct meta-analyses for the CDR-SB and iADRS outcomes and asked the company to add an option to use the results from the meta-analyses in the economic model (clarification question A18b and c).	Further company analyses	No further data collection possible / proposed	Resolution of this uncertainty does not lend itself to further data collection, and would require adjustment to the model.
EAG4	Risk of bias associated with the TRAILBLAZER-ALZ trials and the potential impact on the measurement of the treatment effect		The EAG judged both the TRAILBLAZER-ALZ and TRAILBLAZER-ALZ 2 trials to be of an overall high risk of bias. We considered that the potential for participants and their supporters to become aware of participants' treatment allocation due to ARIA events and infusion-related reactions presented a high risk of bias that could affect the measurement of disease progression based on the CDR-SB in the trials, including the HR from the TRAILBLAZER-ALZ 2 trial that is used in the economic model. Additionally, we had some concerns about impact of risk of bias due to missing outcome data on these outcomes, as there were differences in reasons for participants discontinuing the trials between the trials' arms (e.g. adverse events).	Unquantified	EAG said: We would like the company to provide sensitivity analyses of the hazard ratio, using a Cox proportional hazard model, of disease progression over time to week 76 as measured by the CDR-SB in which participants who experience ARIA or infusion-related reactions or both are censored after the first occurrence (if they have not already experienced disease progression), for both the TRAILBLAZER-ALZ and TRAILBLAZER-ALZ 2 trials. We would also like the company to provide economic model scenario analyses using the hazard ratios for the treatment effect when these participants are censored. It would be desirable if the company also conducted the same sensitivity analyses of the hazard ratios with censoring of these participants when the iADRS is used to measure disease progression.	Further company analyses	No further data collection possible / proposed	Resolution of this uncertainty does not lend itself to further data collection, and would require adjustment to the model.

EAG5	Impact of APOE ε4 allele status	Subgroup analyses of adverse events by APOE ε4 allele status indicate that this allele increases the risk of experiencing an ARIA event for people treated with donanemab. People who are homozygous for the APOE ε4 allele have a greater risk of experiencing ARIA events than people who are heterozygous for this allele and both subgroups have a greater risk than people who are not carriers of this allele	One of our clinical experts advised us that due to the risk of ARIA side effects in homozygous carriers of the APOE ε4 allele, these patients should probably not be treated with donanemab. That expert also commented that the potential risks and benefits of treatment would need to be clearly explained to heterozygous APOE ε4 carriers.	Unquantified	EAG said: We do not suggest an alternative approach. As the number of participants in TRAILBLAZER-ALZ 2 who were homozygous for the APOE ε4 allele is comparatively small (n=213 for the iADRS outcome, n=220 for the CDR-SB outcome) it may not be feasible to obtain a hazard ratio of disease progression for this subgroup that could be used in the economic model	Clinical expert evidence; further data collection	Low	It is not clear from the company's managed access proposal that this uncertainty would be reduced by data collection. However, it is feasible that ongoing data collection may provide sufficient evidence to analyse this subgroup of the population. Testing for this allele status is not expected to be part of the marketing authorisation. The clinical trials and pragmatic RWE studies are not powered to generate estimates of treatment effect within the subgroup of patients with different APOE4 ε4 statuses. As described in Section B.3.2.2 of the NICE submission, APOE4 ε4 status is not considered to be a treatment effect modified based on an interaction test completed using the Cox Proportional Hazards model, which was not statistically significant.
EAG6	Hazard ratios for mortality due to Alzheimer's disease	The company's model applies a single hazard ratio for mortality of 2.55 (relative to the general population mortality) for patients with mild, moderate and severe Alzheimer's disease dementia. The mortality for the general population was applied to patients with MCI due to Alzheimer's disease. In response to clarification question B17b, the company updated their model to include the option to vary the mortality hazard ratio according to the severity of Alzheimer's disease and provided hazard ratios from the NACC dataset to inform this new option.	Previous cost-effectiveness studies of donanemab, other published evidence and clinical expert opinion to the EAG suggest that the risk of death should increase with disease severity and therefore we consider that using a single hazard ratio for different health states may not be reflective of the evidence... We do not consider the NACC hazard ratios to be plausible as these were higher for the mild than the moderate health state. The Crowell study reports hazard ratios for mortality for patients at age 80 years that seem a good approximation to the mortality for a population with a starting age of 73 years (the baseline age in the current model).	High	Ongoing studies in the company's managed access proposal could gather relevant data to resolve this uncertainty. EAG said: The EAG prefers to use mortality hazard ratios that increase with increasing disease severity. We use the mortality hazard ratios from the Crowell study for the 80-year-old subgroup in our base case. We explored the uncertainty around this by conducting alternative scenario analyses using different mortality hazard ratios from the literature	TB-ALZ2-EXT, TB-REAL Global; Clinical expert evidence	Medium	The company's proposed data sources could contribute to reducing this uncertainty in that they each expect to gather long-term clinical uncertainty and safety evidence.

EAG7	Assumptions on the duration of long-term treatment effect	The company's model assumes that the full treatment effect of donanemab observed during the TRAILBLAZER-ALZ 2 trial period is retained for (a) 3.5 years after stopping treatment and then wanes to zero for the following five years (if patients stop after 18 months or due to amyloid clearance); (b) one year after stopping treatment and then wanes to zero for the following 2.5 years (if patients stop due to adverse events). The company's assumptions are based on two main arguments: the time taken to return to amyloid positivity (>24.1CL) after stopping treatment and the relation between amyloid clearance and clinical benefit.	We acknowledge that the results from TRAILBLAZER-ALZ trial show that patients that discontinued treatment at six months due to amyloid clearance have not returned to amyloid positivity at 18 months, i.e., for one year. Also, there is trial evidence for amyloid targeting therapies which indicates a positive correlation between amyloid clearance and clinical efficacy measures, such as CDR-SB scores. However, we note that there is no evidence on the treatment effect beyond the trial period. The clinical experts advising the EAG consider the company's assumptions to be speculative due to lack of available evidence. The assumptions around the duration of the treatment effect have a considerable impact on the model results.	Unquantified	Ongoing studies in the company's managed access proposal could gather relevant data to resolve this uncertainty. EAG said: The EAG assumes that the full treatment effect is retained for a shorter period of one year after stopping treatment (based on trial evidence) and then wanes for the following 2.5 years (in line with the company's assumption that it takes around 3.5 years for patients to return to amyloid positivity) for patients discontinuing treatment after the fixed duration of 18 months, due to amyloid clearance or due to adverse events.	TB-ALZ2-EXT, TB-REAL Global; Clinical expert evidence	High	The company's proposed data sources could contribute to reducing this uncertainty in that they each expect to gather long-term clinical uncertainty and safety evidence.
EAG8	Patient utility values for Alzheimer's disease health states	The company's model uses patient's health state utility values assessed by caregivers using EQ-5D data obtained from the meta-analysis of Landeiro et al. 2020. The pooled estimates of patient utilities combine EQ-5D scores using different countries' value sets	The EAG notes that this is not in line with the NICE Reference Case which states that health state valuations should be derived from a representative sample of the UK population.	Medium	EAG said: The EAG prefers to use EQ-5D scores using a UK value set and therefore we use the proxy-rated patient utilities from the GERAS study in our base case. The GERAS study reported proxy-rated EQ-5D patient utilities assessed by their caregivers for mild, moderate and severe health states. It includes patients from France (n=419), Germany (n=552) and the UK (n=526) but uses the UK value set to calculate patient utilities.	Further discussion on which patient utility estimates are the most appropriate.	No further data collection possible / proposed	Resolution of this uncertainty does not lend itself to further data collection: utility data are usually impractical to obtain during managed access and the company has access to its own EQ-5D data from current sources.

EAG9	Caregiver utility values for Alzheimer's disease health states	The company conducted two vignette studies to derive caregiver utilities using the time trade-off approach, as they argued that the EQ-5D is not sensitive enough to measure the health-related quality of life of caregivers for patients with Alzheimer's disease. The utilities were reported by general population participants.	We note that using time-trade-off utilities reported by general population participants does not meet the criteria for the NICE Reference Case. In our opinion, the company has not provided sufficient convincing evidence to support the use of a different method to derive utilities for use in the economic model	Medium	EAG said: The EAG prefers to use EQ-5D scores directly assessed by caregivers in our base case. The EAG considers that the [GERAS] study utilities meet the NICE Reference Case. As the GERAS study utilities are higher than the utilities for the general population, we have made adjustments to the data used in the model by assuming that caregivers of patients with MCI and mild disease have the same quality of life as the general population based on the age and gender distribution of caregivers in the economic model. For the moderate and severe health states, we adjusted the general population utilities based on the relative decrement between health states observed in the GERAS study. We applied the same utilities regardless of the type of caregiver and the setting where the patient lives. As the evidence is not categorised that way, assumptions would be needed, which would add uncertainty	Further discussion on which caregiver utility estimates are the most appropriate.	No further data collection possible / proposed	Resolution of this uncertainty does not lend itself to further data collection.
MAT1	NHSE resource use	The resource use (patient level, system level) needed to offer this technology to patients is not yet clearly known and is the subject of debate via NHSE.		Unquantified	Real-world evidence from use of technology in NHS would resolve this uncertainty.	RWE from company's planned UK RWE studies; RWE from use in clinical practice under managed access; TB-REAL-Global	High	Either the company's proposed UK RWE studies, and/or RWE derived from use of donanemab in clinical practice during a period of managed access has potential to gather these data. This would require rigorous monitoring to achieve an accurate and complete data set. Note: there is no clinical practice RWE data collection proposed in the company's current managed access proposal, though company-controlled data collection and data from UK SDE(s) are specified.

Trial Data

Are there further relevant trial data that will become available after the NICE evaluation?	
Rating	**Rationale/comments**
High	The main comparative study, and several other studies in the clinical trial programme have finished or will finish within the timeline of this evaluation. The committee should be in position to assess all data from these studies and therefore reach a decision based on a relatively complete data set. However, additional data from TRAILBLAZER-ALZ 2, especially its addendum phases, may develop the evidence significantly in coming years, depending on how data cuts are scheduled. Committee would be able to tie any managed access recommendation to this trial or data cut thereof, according to its data needs. An RWE study has been designed by the company to address a range of the identified uncertainties. Details are currently being revised, though it is intended to establish long-term clinical data, clinical meaningfulness, long-term safety and resource use. It is hoped that NHSE data from an SDE will directly resolve costs and resource use in NHS clinical practice, retrospectively.

TRAILBLAZER-ALZ	
Anticipated completion date	Sep-21
Link to clinicaltrial.gov	https://www.clinicaltrials.gov/study/NCT03367403?intr=Donanemab&limit=100&page=1&rank=9
Start date	Dec-17
Data cut presented to committee	
Link(s) to published data	https://www.nejm.org/doi/full/10.1056/NEJMoa2100708
Description of trial	Assessment of Safety, Tolerability and Efficacy of LY3002813 in Early Symptomatic Alzheimer's Disease. Double blinded, versus placebo. Outcomes include change from baseline in Integrated Alzheimer's Disease Rating Scale (iARDS), same against other rating scales including cognitive/behavioural and physiological. Publication asserts 'better composite score' across assessments but more studies needed. N=272

TRAILBLAZER-EXT	
Anticipated completion date	Mar-24
Link to clinicaltrial.gov	https://www.clinicaltrials.gov/study/NCT04640077?intr=Donanemab&limit=100&aggFilters=status:act&rank=3
Start date	Nov-23
Data cut presented to committee	
Link(s) to published data	None found
Description of trial	Open label extension of TRAILBLAZER-ALZ, n=90

TRAILBLAZER-ALZ 2 (Addendum 11)	
Anticipated completion date	Aug-25
Link to clinicaltrial.gov	https://www.clinicaltrials.gov/study/NCT04437511?intr=Donanemab&limit=100&aggFilters=status:act&rank=1
Start date	Jun-20

Data cut presented to committee	
Link(s) to published data	https://jamanetwork.com/journals/jama/article-abstract/2807533
Description of trial	TRAILBLAZER-ALZ 2 is a Phase 3, double-blind, placebo-controlled study to evaluate the safety and efficacy of N3pG antibody (donanemab) in participants with early symptomatic AD (prodromal AD and mild dementia due to AD) with the presence of brain tau pathology. N=1800 (estimated) Following the double-blind 76-week main study period, a double-blind 78-week long-term extension period is added to further evaluate donanemab efficacy and safety over time. Participants from the addendum safety cohort are not eligible for the extension period. Same measurements as for TRAILBLAZER-ALZ and also pharmacokinetics (average serum concentration of technology) and number or [sic] participants with anti-donanemab antibodies. Results assert donanemab significantly slowed clinical progression at 76 weeks. Annualized mean change in amyloid plaque deposition following the last dose of donanemab as measured by florbetapir F 18 PET - Long-term clinical effectiveness (amyloid reaccumulation)

TRAILBLAZER-ALZ 3	
Anticipated completion date	Nov-27
Link to clinicaltrial.gov	https://www.clinicaltrials.gov/study/NCT05026866?intr=Donanemab&limit=100&aggFilters=status:rec&rank=3
Start date	Aug-27
Data cut presented to committee	
Link(s) to published data	None available (one article located about trial design: https://n.neurology.org/content/100/17_Supplement_2/3010)
Description of trial	The main purpose of this study is to evaluate the safety and efficacy of donanemab in participants with preclinical Alzheimer's Disease (AD). Double blind, randomised against placebo. n= 2600 (Estimated) Range of different assessment criteria including time to clinical progression as measured by Clinical Dementia Rating - Global Score (CDR-GS), International Shopping List Test (ISLT), Continuous Paired Associate Learning (CPAL) and others. Pharmacokinetics and antibodies measured as before.

TRAILBLAZER-ALZ 4	
Anticipated completion date	Sep-23
Link to clinicaltrial.gov	https://www.clinicaltrials.gov/study/NCT05108922?intr=Donanemab&limit=100&aggFilters=status:act&rank=2
Start date	Nov-21
Data cut presented to committee	
Link(s) to published data	https://n.neurology.org/content/100/17_Supplement_2/3126
Description of trial	The main purpose of this study is to compare donanemab to aducanumab on amyloid plaque clearance in participants with early symptomatic Alzheimer's Disease (AD). Randomised allocation, open label design. n=200 (estimated) Primary outcomes: percentage of participants who reach complete amyloid clearance on florbetapir F18 positron emission tomography (PET) scan (superiority) on donanemab versus aducanemab in the overall and in the intermediate populations. Other outcomes measured as previously noted for other trials, but now comparatively against aducanemab. Results assert: 'Significantly higher number of participants reached amyloid clearance and amyloid plaque reductions with donanemab vs. aducanumab at 6 months.'

TRAILBLAZER-ALZ 5

Anticipated completion date	Jun-27
Link to clinicaltrial.gov	https://www.clinicaltrials.gov/study/NCT05508789?intr=Donanemab&limit=100&aggFilters=status:rec&rank=1
Start date	Oct-22
Data cut presented to committee	
Link(s) to published data	None available
Description of trial	TRAILBLAZER-ALZ 5 is a Phase 3, double-blind, placebo-controlled study to evaluate the safety and efficacy of donanemab in participants with early symptomatic AD (prodromal AD and mild dementia due to AD) with the presence of brain tau pathology. n=1500 (estimated) Outcomes equivalent to those recorded in earlier studies.

TRAILBLAZER-ALZ 6	
Anticipated completion date	May-25
Link to clinicaltrial.gov	https://www.clinicaltrials.gov/study/NCT05738486?intr=Donanemab&limit=100&aggFilters=status:rec&rank=2
Start date	Feb-23
Data cut presented to committee	
Link(s) to published data	None available
Description of trial	This study will investigate different donanemab dosing regimens and their effect on the frequency and severity of amyloid-related imaging abnormality - Edema/Effusion (ARIA-E) in adults with early symptomatic Alzheimer's disease (AD) and explore participant characteristics that might predict risk of ARIA. n=800 (estimated) Primary outcomes is percentage of participants with ARIA-E and secondary outcomes are equivalent to earlier studies.

TB-REAL-Global - Long-term comparative effectiveness study	
Anticipated completion date	During 2029
Link to clinicaltrial.gov	-
Start date	During 2026
Data cut presented to committee	-
Link(s) to published data	-
Description of trial	To compare the effect of donanemab and Usual Care versus Usual Care alone on dependence level in participants with early symptomatic AD. The outcomes are: (i) Function (FAQ); (ii) Quality of Life (QoL-AD); (iii) Time to loss of Independence (SDS); (iv) Time to Institutionalization/Mortality; (v) Caregiver Burden (ZBI). PET sub-study aims to determine the proportion of participants who reach amyloid clearance, and to assess amyloid reduction rates and change in amyloid over time. Company aims to resolve long-term clinical uncertainty, confirm clinical meaningfulness, establish long-term safety and resource use, and HRQoL with this study.

UK Real World Evidence HCRU Studies	
Anticipated completion date	Q4 2026
Link to clinicaltrial.gov	-
Start date	Q4 2024
Data cut presented to committee	-
Link(s) to published data	-

Description of trial	Retrospective study aiming to: "Generate evidence to inform resource use in health and social care for patients with MCI due to AD and AD dementia" and gather "Patient characteristics, diagnostic experience, and treatment journey in patients with MCI due to AD and AD dementia". This will be the key RWE study resolving uncertainty around cost and resource use in NHS clinical practice. This retrospective RWE study is being fully funded by Eli Lilly and is being carried out in collaboration with a Secure Data Environment (SDE) provider. No collaboration or funding from NHSE is required. Primary Objectives i. Describe the demographic and clinical characteristics of patients diagnosed with mild cognitive impairment (MCI) and mild, moderate and severe AD ii. Estimate the total health-care resource use (HCRU) incurred by AD patients within each stage of disease, stratified by direct healthcare cost, social care cost and informal care cost (if available) iii. To estimate the impact of a slowing of disease progression in terms of resource use, costs, dependency and care level Secondary Objectives The secondary objective is to investigate the association between baseline patient characteristics and HCRU at the later stage of AD. Exploratory Objectives The exploratory objective is to estimate the impact of a slowing of disease progression in terms of resource use, dependency and care level

UK Controlled Access Programme	
Anticipated completion date	-
Link to clinicaltrial.gov	-
Start date	-
Data cut presented to committee	-
Link(s) to published data	-
Description of trial	To register all patients prior to initiation of donanemab, promoting the safe and effective use of the donanemab Patient age, sex, APOE4 status, medical history, concomitant medications, AD stage at initiation, method of amyloid confirmation

Data collected in clinical practice

Is RWE data collection within managed access feasible?	
Overall Rating	**Rationale/comments**
Medium	There are no current robust, NHSE-wide RWE sources set-up that could collect data for this indication. NHSE has expressed that new, mandated NHSE-wide data collection is not currently in its plans. Therefore, any RWE for this topic will be provided by the company. In its managed access proposal, the company describes a global RWE study (TB-REAL) in early stages (see Trial Data tab for more information), and other evidence sources: 1) Comparative long-term effectiveness studies comprising TB-REAL are to be carried out in the US and Europe, which will provide long-term real-world evidence of patients treated with donanemab compared with a matched placebo cohort 2) A study (UK HCRU study) will be conducted using data from a UK secure data environment, and potentially expanded to a second, in two phases. These data will be gathered at multiple time points, before and after the introduction of donanemab to understand costs of treatment with BSC and donanemab related to severity of disease. These data are not UK-wide but provide something of an internal control arm. 3) Two registries have been cited (PEARL and InRAD) that have potential to gather useful data but these are either not in UK populations and not tailored to the committee's uncertainties, or not yet collecting data. It is not clear how complete the data will be or what quality will be available.

Data Source		
Relevance to managed access		
Existing, adapted, or new data collection	New	
Prior experience with managed access	Low	
Relevance of existing data items	Low	
If required, ease that new data items can be created / modified	Not applicable	
How quickly could the data collection be implemented	Unclear	
Data quality		
Population coverage	Low	
Data completeness	Low	
Data accuracy	Medium	Varies between very high for UK SDE and unknown for registries
Data timeliness	Medium	Varies between very high for UK SDE and unknown for registries
Quality assurance processes	Medium	Varies between very high for UK SDE and unknown for registries
Data availability lag	Medium	Varies between very high for UK SDE and unknown for registries
Data sharing / linkage		
New data sharing arrangements required?	Unclear	
New data linkages required?	Unclear	
If yes, has the governance of data sharing been established	Unclear	
Analyses		
How easily could collected data be incorporated into an economic model	Medium	Company appears confident, SAP would be needed during MAA implementation phase
Existing methodology to analyse data	Yes	

If no, is there a clear process to develop the statistical analysis plan	Unclear	
Existing analytical capacity	High	Conducted by company
Governance		
Lawful basis for data collection	Yes	Appears to be covered by current ways of working for various data sources
Privacy notice & data subject rights	Unclear	TBC
Territory of processing	Unclear	TBC
Data protection registration	Unclear	TBC
Security assurance	Unclear	TBC
Existing relevant ethics/research approvals	Unclear	TBC
Patient consent	Unclear	TBC
Funding		
Existing funding	Not applicable	From company sources
Additional funding required for MA	Unclear	
If yes, has additional funding been agreed in principle	Unclear	
Service evaluation checklist - registry specific questions		
HRA question 2. Does the study protocol demand changing treatment/care/services from accepted standards for any of the patients/service users involved?		
Does data collection through registry require any change from normal treatment or service standards?	Yes	
Are any of the clinical assessments not validated for use or accepted clinical practice	No	
HRA question 3. Is the study designed to produce generalisable or transferable findings?		
Would the data generated for the purpose of managed access be expected to be used to make decisions for a wider patient population than covered by the marketing authorisation / NICE recommendation	No	
Additional considerations for managed access		
Are the clinical assessments and data collection comparable to current clinical practice data collection?	Yes	
Burden		
Additional patient burden	No	
Additional clinical burden	Yes	
Other additional burden	Yes	

Other issues

Explanation

This page details the Managed Access Team's assessment on whether there are any potential barriers to agreeing a managed access agreement and that any potential managed access agreement operates according to the policy framework developed for the Cancer Drugs Fund and Innovative Medicines Fund.

The items included are informed by the relevant policy documentation, expert input from stakeholders including the Health Research Authority, and the Managed Access team's experience with developing, agreeing and operating managed access agreements. Additions or amendments may be made to these considerations as further experience is gained from Managed Access.

The Managed Access Team will justify it decision, but broadly it is a matter of judgement on whether any issues identified, taken as a whole, are likely to lead to a barrier to a Managed Access Agreement being agreed, or operationalised in the NHS. No assessment is made whether a Commercial Access Agreement is likely to be reached between the company and NHS England, which could be a substantive barrier to managed access.

Are there any substantive issues (excluding price) that are a barrier to a MAA	
Overall rating	**Rationale/comments**
Yes - Major	High burden from any new data collection arrangements; implementation would be burdensome in routine commissioning and managed access; restricted implementation would go against IMF principles; complexity of topic would likely delay DCA development.

		Rating	Rationale / comments
Burden	Expected overall additional patient burden from data collection?	High	Data collection within current practice does not exist and therefore there would be additional burden. Collection would need to be in primary and secondary care, which would be complex to implement.
	Expected overall additional system burden from data collection?	High	Data collection within current practice does not exist and therefore there would be additional burden. Collection would need to be in primary and secondary care, which would be complex to implement.
	Do stakeholders consider any additional burden to be acceptable		Would need to check with NHSE in particular
	Would additional burden need to be formally assessed, and any mitigation actions agreed, as part of a recommendation with managed access	Yes	This is unclear

		Rating	Rationale / comments
Patient Safety	Have patient safety concerns been identified during the evaluation?		TBC
	Is there a clear plan to monitor patient safety within a MA?		TBC
	Are additional patient safety monitoring processes required	No	Unlikely to require safety monitoring further than what would be expected in routine commissioning

		Rating	Rationale / comments
Patient access after MAA	Are there are any potential barriers to the agreed exit strategy for managed access, that in the event of negative NICE guidance update people already having treatment may continue at the company's cost		IMF principles say that in the event of a negative recommendation at exit treatment will continue at the company's cost. The large budget impact may affect the company's willingness to enter managed access.
	If yes, have NHS England and the company agreed in principle to the exit strategy		TBC

		Rating	Rationale / comments
Service implementation	Is the technology disruptive to the service	No	Disruption would be the same for routine commissioning and managed access. Therefore, managed access would not subject system to additional burden, as things stand.
	Will implementation subject the NHS to irrecoverable costs?	Yes	Implementation through routine commissioning or managed access would be expensive and resource-intensive.

	Is there an existing service specification which will cover the new treatment?	Unclear	Service for this treatment would be a significant deviation to current care.

		Rating	Rationale / comments
Patient eligibility	Are there specific eligibility criteria proposed to manage clinical uncertainty	Unclear	Will depend on committee decision making. IMF principles dictate that the treatment needs to be made available to the entire eligible population for the indication.
	If yes, are these different to what would be used if the technology had been recommended for routine use?	Not applicable	

		Rating	Rationale / comments
Service evaluation checklist	HRA question 1. Are the participants in your study randomised to different groups?		
	Will the technology be available to the whole recommended population that meet the eligibility criteria?	No	Current discussions suggest implementation will be limited at first.
	HRA question 2. Does the study protocol demand changing treatment/care/services from accepted standards for any of the patients/service users involved?		
	Will the technology be used differently to how it would be if it had been recommended for use?	Unclear	There may be differences in how the drug would be rolled in managed access to routine commissioning but this is unclear.
	Any issues from registry specific questions	No	
	HRA question 3. Is the study designed to produce generalisable or transferable findings?		
	Any issues from registry specific questions	No	
	Additional considerations for managed access		
	Is it likely that this technology would be recommended for routine commissioning disregarding the cost of the technology?	Unclear	Difficult to assess for this indication
	Any issues from registry specific questions	No	No suitable registry identified

		Rating	Rationale / comments
Equality	Are there any equality issues with a recommendation with managed access	Unclear	Restricted implementation could have equality issues

		Rating	Rationale / comments
Timings	Likelihood that a Data Collection Agreement can be agreed within normal FAD development timelines	Unclear	What data could be collected would depend on how the drug is implemented, and if delayed would delay any DCA development