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 **Comments on the Draft Guidance from Eli Lilly and Company**
   a. Draft guidance comments
   b. Additional queries response
   c. Evans et al 2023: TRAILBLAZER-EXT longer-term effects of donanemab

2. **Consultee and commentator comments on the Draft Guidance** from:
   a. Alzheimer's Research UK
   b. Alzheimer's Society
   c. Association of British Neurologists
   d. College of Mental Health Pharmacy
   e. Faculty of Public Health
   f. Royal College of Psychiatrists
   g. UK Clinical Pharmacy Association
   h. NHS England response on infusion pricing and treatment duration
   i. Eisai

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 **Comments on the Draft Guidance received through the NICE website**

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 **External Assessment Group critique of company comments on the Draft Guidance**

5. **Eli Lilly and Company 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.

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Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on Wednesday 20 November. 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
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]

NICE National Institute for Health and Care Excellence

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<table>
<tr><th>Comment number</th><th>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.</th></tr>
<tr><td>1</td><td>
Executive summary
Lilly welcomes the opportunity to comment on the preliminary recommendation made by the appraisal committee detailed in the draft guidance consultation document 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.

Changes to marketing authorisation
Since the original submission to NICE in February 2024 which was based on the anticipated marketing authorisation wording at that time, marketing authorisation for donanemab has been granted by the Medicines and Healthcare products Regulatory Agency (MHRA).[1] The confirmed indication wording is now available and the differences are highlighted in Table 1.

Table 1: Updates to marketing authorisation
<table>
<tr><th></th><th>Anticipated label</th><th>Confirmed label</th></tr>
<tr><td>Indication</td><td>[redacted]</td><td>Donanemab is indicated for the treatment of mild cognitive impairment and mild dementia due to AD in adult patients that are apolipoprotein E ε4 (APOE4) heterozygotes or non-carriers.</td></tr>
</table>
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Contraindications	None specified	Imaging findings suggestive of Cerebral Amyloid Angiopathy (CAA) that increase the risk of amyloid-related imaging abnormalities (ARIA) or intracerebral haemorrhage (acute or subacute cerebral haemorrhage, superficial siderosis, more than 4 microhaemorrhages, severe white matter disease, pre-treatment magnetic resonance imaging [MRI] showing ARIA-oedema/effusion [ARIA-E], previous cerebral haemorrhage or previous subarachnoid haemorrhage unless it is no longer at risk of re-bleeding). Treatment with donanemab should not be initiated in patients receiving ongoing anticoagulant therapy.
Stopping rule	None specified	…if a patient progress to moderate AD before the end of the 18 months maximum treatment, donanemab should be stopped.

In line with the final marketing authorisation, updated clinical data in the relevant patient population have been provided in Table 2.

Table 2: Clinical outcomes from baseline to 76 weeks in the UK eligible population (TB2 only)

Outcome[a]	Statistical method	Donanemab			Placebo			LSM difference vs placebo (95% CI)	p value vs placebo	Slowing of clinical progression %[b]
		Mean (SD)		LSM change (95% CI)	Mean (SD)		LSM change (95% CI)			
		Baseline	76 Weeks		Baseline	76 Weeks				
iADRS		[redacted]	[redacted]		[redacted]	[redacted]				
	NCS2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	<.001	[redacted]
	MMRM[c]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	<0.0001	[redacted]
CDR-SB		[redacted]	[redacted]		[redacted]	[redacted]				
	NCS2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	<.001	[redacted]
	MMRM[c]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	<0.0001	[redacted]

Footnotes: [a]Clinical outcomes were scored as follows: CDR-SB range from 0 to 18, with higher scores indicating greater clinical impairment; iADRS range from 0 to 144, with lower scores indicating greater impairment.
[b]The percentage of slowing of clinical progression was calculated by dividing the LSM change from baseline treatment differences at 76 weeks by the LSM change from baseline with placebo at 76 weeks and multiplying by 100. [c]For MMRM analyses, 95%CIs for LSM changes were calculated with the normal approximation method.
Abbreviations: CDR-SB: sum of boxes of the Clinical Dementia Rating Scale; CI: confidence interval; iADRS: Integrated Alzheimer Disease Rating Scale; LSM: least-squares mean; MMRM: mixed models for repeated measures; NCS2: natural cubic spline with 2 degrees of freedom; SD: standard deviation; TB2: TRAILBLAZER-ALZ 2.

Updated patient access scheme

An updated patient access scheme (PAS) has been proposed for donanemab. The proposed donanemab price with the updated PAS discount of [redacted] applied is [redacted] per vial.

Revised base case results following DGD

As part of the draft guidance response, Lilly have provided the results of the company revised base case following draft guidance document (DGD) in Table 3. This incorporates the updated clinical data described in Table 5 as well as the following assumptions:

- The proportion of patients starting the model in the MCI due to AD and mild AD dementia health states has been updated (Comment 10)
- A differential mortality risk between stages of AD has been applied, using the company National Alzheimer's Coordinating Centre (NACC) analysis as the source of mortality data (Comment 5)
- A stopping rule on progression to the moderate AD health state has been implemented in line with the updated label (Comment 3)
- A revised source informing the risk of transitioning to residential care per cycle, in line with EAG base case (Comment 11)
- Neurologist outpatient visit included in the cost of APOE-4 testing, in line with EAG base case
- Inclusion of one neurologist outpatient visit per cycle as a follow-up visit to monitor disease progression, in line with EAG base case
- No terminal care costs are included, in line with committee preference at ACM1 and EAG base case

The revised base case following DGD probabilistic cost-effectiveness results for donanemab versus established clinical management run with 1,000 iterations are presented in Table 3, and deterministic base case results are presented in Table 4. 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 incremental cost-effectiveness ratio (ICER) of £12,787.

Table 3: Summary of company revised probabilistic base case following DGD results (revised donanemab PAS price at DGD 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]	£12,787

Abbreviations: ICER: incremental cost-effectiveness ratio; NHB: net health benefit; QALY: quality-adjusted life year.

Table 4: Summary of company revised deterministic base case following DGD results (revised donanemab PAS price at DGD 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]	£12,091

Abbreviations: ICER: incremental cost-effectiveness ratio; NHB: net health benefit; QALY: quality-adjusted life year.

2

Additional estimates from TRAILBLAZER-AZ 2 and from the meta-analyses of TRAILBLAZER-ALZ 2 and TRAILBLAZER-ALZ for CDR-SB and iADRS for the UK eligible population and by APOE4 status

In response to the request, a meta-analysis of TRAILBLAZER-ALZ 2 and TRAILBLAZER was performed, using data in the UK eligible population from the trials as per the population described in the updated marketing authorisation.

Using the pooled individual data from TRAILBLAZER-ALZ 2 and TRAILBLAZER-ALZ, the hazard ratio (HR) of progressing to clinical worsening between donanemab and BSC was estimated using the same Cox proportional hazard (CPH) model as originally pre-specified in the study TRAILBLAZER-ALZ 2 statistical analyses plan:

- The progression to clinical worsening between donanemab and BSC was defined as a 1-point or more increase in Clinical Dementia Rating–Sum of Boxes (CDR-SB) (5-point or more decrease in iADRS) from baseline for participants with baseline clinical status of MCI due to AD, or a 2-point increase (9-point or more decrease in iADRS) from baseline for participants with baseline clinical status of mild AD dementia at 2 consecutive visits; the analyses used the first event for modelling, with the following updates:
  - Restricted to UK eligible patients, i.e., excluding APOE4 homozygotes patients, patients with missing APOE4 status, and patients with anticoagulants
  - The same variables in the a priori defined Cox model were used with the addition of the study variable. The same model was run with the interaction study*study treatment. As this interaction was not statistically significant (p=0.2137 for CDR-SB and p=0.8326 for iADRS), the interaction was removed from the model.
  - The pooled investigator variable from TRAILBLAZER-ALZ was rederived as performed in TRAILBLAZER-ALZ 2

The HRs versus best standard of care derived for disease progression as measured by CDR-SB scale and Integrated Alzheimer's Disease Rating Scale (iADRS) in patients with MCI due to AD, mild–moderate AD dementia are presented in Table 5.

Table 5: Hazard ratios of disease progression for donanemab versus BSC (CDR-SB scale and iADRS scale)

	CDR-SB HR (95% CI) vs BSC	iADRS HR (95% CI) vs BSC
Original analyses on the overall TRAILBLAZER-ALZ 2 population	0.623 (0.519, 0.748)	0.700 (0.582, 0.842)
UK eligible population in TRAILBLAZER-ALZ 2	[redacted]	[redacted]
UK eligible population in TRAILBLAZER-ALZ 2 censoring patients at their first occurrence of ARIA/IRR on the UK eligible population	[redacted]	[redacted]
Meta-analysis of TRAILBLAZER-ALZ 2 and TRAILBLAZER-ALZ on the UK eligible population	[redacted]	[redacted]

Meta-analysis of TRAILBLAZER-ALZ 2 and TRAILBLAZER-ALZ censoring patients at their first occurrence of ARIA/IRR on the UK eligible population	[redacted]	[redacted]

Abbreviations: BSC: best standard of care; CDR-SB: Clinical Dementia Rating Scale – Sum of Boxes; HR: hazard ratio; iADRS: Integrated Alzheimer's Disease Rating Scale.

As highlighted in the company's response to the EAG's clarification question A18, the study design of the two studies included in the meta-analysis differ: the TRAILBLAZER-ALZ trial only includes patients with low-medium tau, some exclusion criteria differ such as historical/existing medical conditions and prior/concomitant therapy, and the rules to assess the ability to stop treatment differ between the two studies, all of which mean the outcome of a meta-analysis of the trials should be interpreted with caution. The results from the meta-analyses are similar to the stand-alone results from TRAILBLAZER-ALZ 2, which is expected given the much smaller sample size from the TRAILBLAZER-ALZ trial.

For these reasons, the use of the HR for disease progressions as measured by CDR-SB derived from TRAILBLAZER-ALZ 2 alone within the model is considered more appropriate than using the HR from the meta-analysis due to the consistency of the data source. Use of the meta-analysis within the economic model is explored within a scenario analysis, presented in Table 6.

Table 6: Scenario analyses (revised donanemab PAS price at DGD response) – Alternative clinical data sources

Technologies	Inc. costs (£)	Inc. QALYs	ICER (£/QALY)
Revised base case following DGD: Clinical data taken from TRAILBLAZER-ALZ 2	[redacted]	[redacted]	£12,091
Clinical data taken from the meta-analysis of TRAILBLAZER-ALZ 2 and TRAILBLAZER-ALZ	[redacted]	[redacted]	£14,618

Abbreviations: HR: hazard ratio; ICER: incremental cost-effectiveness ratio; Inc. incremental; PAS: patient access scheme; QALY: quality-adjusted life year.

The meta-analyses were run with the same models as previously described for TRAILBLAZER-ALZ 2, with the addition of the study variable as a covariate. Clinical outcomes from the meta-analysis are presented in Table 7.

Table 7: Clinical outcomes from baseline to 76 weeks in the UK eligible population (TB1 + TB2 meta-analysis)

Outcome[a]	Statistical method	Donanemab		Placebo		LSM difference	p value	Slowing of
		Mean (SD)		Mean (SD)				

		Baseline	76 Weeks	LSM change (95% CI)	Baseline	76 Weeks	LSM change (95% CI)	vs placebo (95% CI)	vs placebo	clinical progression %[b]
iADRS		[redacted]	[redacted]		[redacted]	[redacted]				
	NCS2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	<0.001	[redacted]
	MMRM[c]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	<0.0001	[redacted]
CDR-SB		[redacted]	[redacted]		[redacted]	[redacted]				
	NCS2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	<0.001	[redacted]
	MMRM[c]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	<0.0001	[redacted]

Footnotes: [a]Clinical outcomes were scored as follows: CDR-SB range from 0 to 18, with higher scores indicating greater clinical impairment; iADRS range from 0 to 144, with lower scores indicating greater impairment.
[b]The percentage of slowing of clinical progression was calculated by dividing the LSM change from baseline treatment differences at 76 weeks by the LSM change from baseline with placebo at 76 weeks and multiplying by 100. [c]For MMRM analyses, 95%CIs for LSM changes were calculated with the normal approximation method.
Abbreviations: CDR-SB: sum of boxes of the Clinical Dementia Rating Scale; CI: confidence interval; iADRS: Integrated Alzheimer Disease Rating Scale; LSM: least-squares mean; MMRM: mixed models for repeated measures; NCS2: natural cubic spline with 2 degrees of freedom; SD: standard deviation; TB1: TRAILBLAZER-ALZ; TRAILBLAZER-ALZ 2.

In order to investigate the impact of APOE4 allele status, both the APOE4 allele status variable and its interaction with the study treatment were incorporated into the previously described Cox model.

The interactions number of APOE4 allele by study treatment were not statistically significant for the CDR-SB and iADRS. Therefore, the distinction between APOE4 non-carrier patient and APOE4 heterozygous patients is not considered as a factor that modifies the effect of the treatment. The

HR for both subgroups are displayed in Table 8, showing similar hazard ratios and associated 95% confidence intervals for APOE4 non-carrier patients and APOE4 heterozygote patients.

Table 8: Hazard ratios of disease progression for donanemab versus BSC (CDR-SB scale and iADRS scale) per APOE4 allele status on the UK eligible population

	CDR-SB HR (95% CI) vs BSC	iADRS HR (95% CI) vs BSC
TRAILBLAZER-ALZ 2 UK eligible population		
Non-carriers	[redacted]	[redacted]
Heterozygotes	[redacted]	[redacted]
Meta-analysis of TRAILBLAZER-ALZ 2 and TRAILBLAZER-ALZ UK eligible population		
Non-carriers	[redacted]	[redacted]
Heterozygotes	[redacted]	[redacted]

Abbreviations: BSC: best standard of care; CDR-SB: Clinical Dementia Rating Scale – Sum of Boxes; HR: hazard ratio; iADRS: Integrated Alzheimer's Disease Rating Scale.

The least-squares mean change from baseline at Week 76 differences between placebo and donanemab are also presented by APOE4 status in Table 9 for the NCS2 analyses and in Table 10 for the MMRM analyses. As for the HR analyses, all interactions between APOE4 status by study treatment (by each spline for the NCS2 models and by visit for the MMRM models) were not statistically significant. There is, therefore, no evidence that the APOE4 status (non-carrier patients vs heterozygous patients) is a treatment effect modifier.

Table 9: NCS2 least-square mean change from baseline at Week 76 differences between donanemab and BSC (CDR-SB scale and iADRS scale) per APOE4 allele status on the UK eligible population

	CDR-SB LSM change (95% CI) vs BSC	iADRS LSM change (95% CI) vs BSC
TRAILBLAZER-ALZ 2 UK eligible population		
Non-carriers	[redacted]	[redacted]

	Heterozygote	[redacted]	[redacted]
	Meta-analysis of TRAILBLAZER-ALZ 2 and TRAILBLAZER-ALZ UK eligible population		
	Non-carriers	[redacted]	[redacted]
	Heterozygote	[redacted]	[redacted]

Footnotes: Clinical outcomes were scored as follows: CDR-SB range from 0 to 18, with higher scores indicating greater clinical impairment; iADRS range from 0 to 144, with lower scores indicating greater impairment.
Abbreviations: APOE4: apolipoprotein E ε4; CDR-SB: sum of boxes of the Clinical Dementia Rating Scale; CI: confidence interval; iADRS: Integrated Alzheimer Disease Rating Scale; LSM: least-squares mean; NCS2: natural cubic spline with 2 degrees of freedom; SD: standard deviation.

Table 10: MMRM least-square mean change from baseline at Week 76 differences between donanemab and BSC (CDR-SB scale and iADRS scale) per APOE4 allele status on the UK eligible population

	CDR-SB LSM change (95% CI) vs BSC	iADRS LSM change (95% CI) vs BSC
TRAILBLAZER-ALZ 2 UK eligible population		
Non-carriers	[redacted]	[redacted]
Heterozygote	[redacted]	[redacted]
Meta-analysis of TRAILBLAZER-ALZ 2 and TRAILBLAZER-ALZ UK eligible population		
Non-carriers	[redacted]	[redacted]
Heterozygote	[redacted]	[redacted]

Footnotes: APOE4: apolipoprotein E ε4; Clinical outcomes were scored as follows: CDR-SB range from 0 to 18, with higher scores indicating greater clinical impairment; iADRS range from 0 to 144, with lower scores indicating greater impairment. For MMRM analyses, 95%CIs for LSM changes were calculated with the normal approximation method.
Abbreviations: CDR-SB: sum of boxes of the Clinical Dementia Rating Scale; CI: confidence interval; iADRS: Integrated Alzheimer Disease Rating Scale; LSM: least-squares mean; MMRM: mixed models for repeated measures; SD: standard deviation.

3	**Treatment stopping rule at 18 months as informed by monitoring of amyloid clearance**

As noted in the company submission and according to the label, patients can receive donanemab according to a fixed dose duration for 18 months or treat-to-clear for up to a maximum of 18 months, as informed by amyloid clearance detected on amyloid-positron emission tomography (PET) imaging. The ratio of patients following each of these dosing strategies was estimated to be in a ratio of 90%:10%. However, the EAG had assumed that all patients receiving donanemab would be treated for the full duration of 18 months with no patients assumed to be on a treat-to-clear strategy. Although availability of PET scanners in the UK is limited, the company does not believe this to be an accurate assumption as some utilisation does occur and is likely to increase in the future. Additionally, the use of donanemab is expected within specialist sites that already have PET scanning capability and the necessary infrastructure in place. Access to PET scanners is a key barrier in delivering disease-modifying therapies via treat to clear (TTC), and clinical expert opinion suggests that many would pursue this route if access to PET scanning capabilities was available.

The proportion of patients in the company model following the treat-to-clear strategy (10%) was informed by clinical opinion on PET scanner and tracer capacity in the UK. There is currently a lack of available data on exact UK usage; this is because there are currently no disease-modifying therapies available in the UK, so there is no need for routine amyloid testing at present. Results from an online survey, with responses from 17% of UK Nuclear Medicine sites, indicate that PET scanners are currently used to monitor amyloid levels in AD in at least 13 UK centres,[2] so the EAG's assumption that a treat-to-clear stopping rule would not be feasible is overly conservative. Additionally, as the committee noted that the NHS England submission estimated that 15% of people would have an amyloid-PET scan, it can be assumed that monitoring will be available in some capacity in the UK, although it is acknowledged that the exact level is uncertain.

For these reasons it can confidently be assumed that the availability of PET scanners in the UK will be non-zero – therefore in the revised base case following DGD 10% of patients will follow the TTC strategy, being monitored for amyloid clearance at 6 months or 12 months, with all patients stopping treatment by 18 months. Scenario analyses exploring 15% of patients following the TTC strategy and 0% of patients following the TTC strategy (all patients treated for a fixed duration of 18 months), in line with National Health Service (NHS) England and the EAG's estimates respectively, are presented in Table 11. The numbers of patients stopping treatment included in the model derived from the numbers achieving amyloid clearance in the TRAILBLAZER-ALZ 2 trial. These results demonstrate that this assumption has a limited impact on the cost-effectiveness results and therefore, is not a key source of uncertainty within the analysis.

Table 11: Scenario analyses (revised donanemab PAS price at DGD response) – Positive stopping rule / TTC strategy

Technologies	Inc. costs (£)	Inc. QALYs	ICER (£/QALY)

Revised base case following DGD: 10% of patients follow the TTC strategy	[redacted]	[redacted]	£12,091
0% of patients follow the TTC strategy (all patients treated for a fixed duration of 18 months)	[redacted]	[redacted]	£12,490
15% of patients follow the TTC strategy	[redacted]	[redacted]	£11,888

Abbreviations: ICER: incremental cost-effectiveness ratio; Inc. incremental; PAS: patient access scheme; QALY: quality-adjusted life year; TTC: treat to clear.

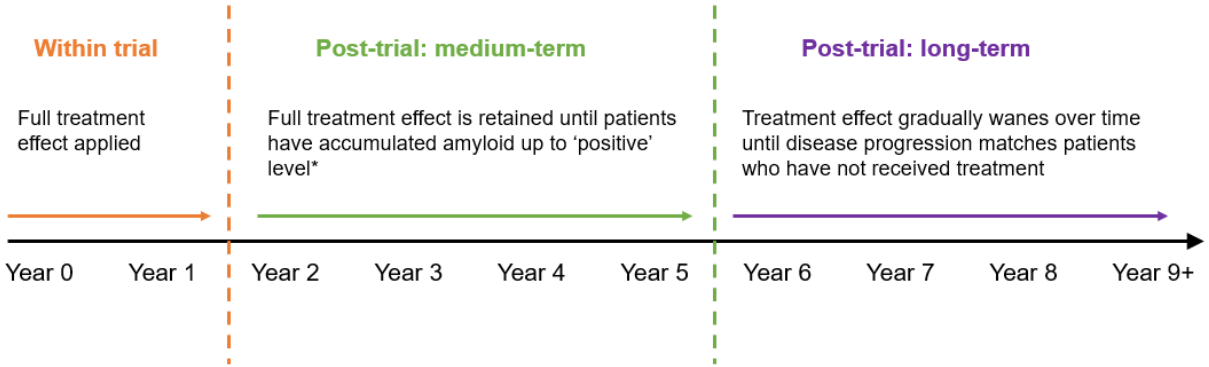
4

Further information on the treatment waning assumptions within the model

During ACM1, the committee acknowledged that the long-term clinical effects of donanemab were unknown and requested that further justification be provided and additional scenario analyses explored.

The conceptual approach to the modelling of treatment effect is presented in Figure 1.

Figure 1: Conceptual approach to modelling of treatment effect

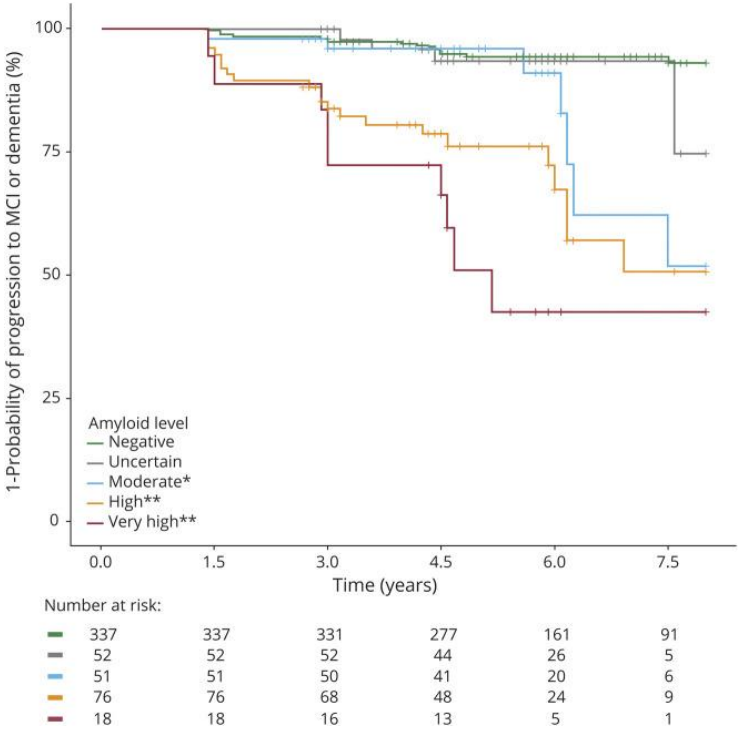


*Amyloid positivity is defined as an amyloid plaque level >24.1 CL.[3]

With the clinical data presented in the original submission (representative of the anticipated marketing authorisation) and based on amyloid levels at Week 76 in TRAILBLAZER-ALZ 2 and using a reaccumulation rate of 2.8 centiloids (CL) per year (derived from TRAILBLAZER trial data),[4] the time

	taken for a return to an amyloid plaque level >24.1 CL, which equates to amyloid positivity, after last treatment is approximately 3.5 years, assuming linear increase over time. However, with the updated clinical data (reflective of the confirmed marketing authorisation), the time taken for a return to an amyloid plaque level >24.1 CL is approximately 4 years. Lilly consider that the EAG's approach is highly unrealistic as it assumes that, once a patient reaches an amyloid plaque level of 24.1 CL, all treatment effect is immediately lost. Published research indicates that this is not the case, with van der Kall et al. (2021) reporting that patients with an amyloid plaque level of 26–50 CL at baseline showed little clinical progression until 4.5 years of follow-up (Figure 2).[5, 6] Quenon et al. (2024) reported in a study of 1,321 patients that an intermediate amyloid burden defined as 12–50 CL was not associated with an increased risk of clinical progression after 3.4 years.6 Additionally, Sperling et al (2024) reported that patients with an amyloid plaque level <46.1 CL showed minimal functional decline, and patients with amyloid plaque levels of between 46.1–77.2 CL at baseline demonstrated decline at later timepoints over 4.5 years compared with patients with amyloid plaque levels of >77.2 CL.[7]

Figure 2: Kaplan-Meier survival analysis by amyloid level (van der Kall et al. 2021)



Amyloid levels: Negative: <15 CL; Uncertain: 15–25 CL; Moderate: 26–50 CL; High: 51–100 CL; Very high: >100 CL.
Abbreviations: MCI: mild cognitive impairment.

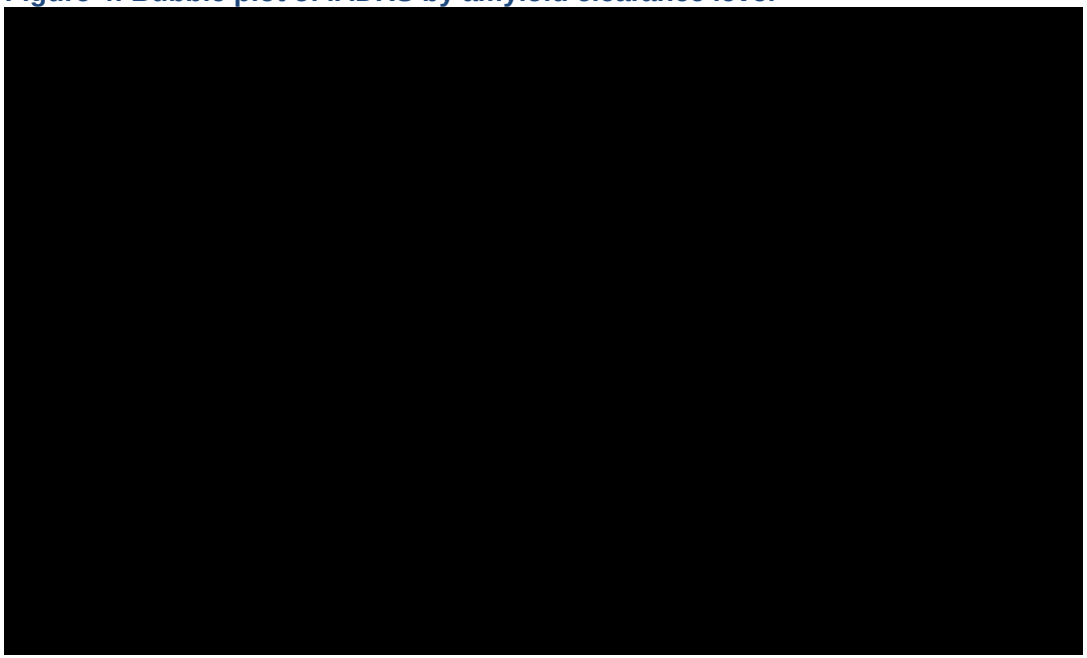
Assuming residual treatment effect at an amyloid plaque level >24.1 CL, it would take approximately 9 years to reach an amyloid level of 50 CL at a reaccumulation rate of 2.8 CL per year, and so the company base case has been revised following DGD to gradual waning over 9 years in line with this level. It is worth noting that in TRAILBLAZER-ALZ 2, the baseline amyloid plaque levels were 103.5 CL in the donanemab arm and 101.6 CL in the placebo arm, which would require ~28 years of reaccumulation from 24.1 CL to reach this level of amyloid burden at a rate of 2.8 CL per year.

	This demonstrates that the EAG's assumption does not reflect the available clinical evidence and that the estimate within the company submission that the full treatment effect of donanemab would be maintained until amyloid plaque levels reach 24.1 CL is already conservative. In addition to this, the reduction of amyloid to levels that prevent promotion of the spread of tau pathology, and therefore neurodegeneration, would provide a therapeutic benefit until the threshold is reached upon reaccumulation. Knopman et al analysed the increase in tau PET flortaucipir signal in four regions of interest (entorhinal, inferior temporal, lateral parietal and a meta-region) in 167 cognitively normal participants who were allocated to four groups according to amyloid status: low, <−8 CL; subthreshold, 9–21 CL; suprathreshold, 22–67 CL; and high, >68 CL.[8] They demonstrated that only in the >68 CL group was there a significant increase in annualised change in tau PET standardised uptake value ratio (SUVR), and that it is an increase in tau PET, rather than Aβ elevation, that is temporally linked to overt cognitive impairment. These results are consistent with modelling simultaneously of Pittsburgh compound B (PIB) SUVR, flortaucipir SUVR, and cortical thickness which showed that decline in memory performance in patients who were cognitively normal occurred largely when Aβ levels exceeded 68 CL.[9] The Aβ value of 68 CL or more, associated with flortaucipir accumulation, was in the range between MCI and dementia in a recent imaging-pathological study.[10] Sperling et al (2024) also indicated that the degree of amyloid burden is the strongest predictor of functional decline. They demonstrated a dose-dependent impact of increasing centiloid burden on CDR-SB, with the greatest decline observed in patients with amyloid plaque levels of >77.2 CL.[7] Figure 3 and Figure 4 show the CDR-SB and iADRS results from TRAILBLAZER-ALZ 2 trial, further supporting the dose dependent increase of amyloid plaque levels and functional decline.

Figure 3: Bubble plot of CDR-SB by amyloid clearance level

Abbreviations: CDR-SB: Clinical Dementia Rating Scale – Sum of Boxes; CL: centiloids; LS: least square.

Figure 4: Bubble plot of iADRS by amyloid clearance level



Abbreviations: CDR-SB: Clinical Dementia Rating Scale – Sum of Boxes; CL: centiloids; LS: least square.

Table 12: Summary of approach to long-term treatment effect within the model

	Original company base case	EAG base case	Revised company base case following DGD
Within trial	Full effect maintained for 18 months		
Post-trial: medium term	Full effect maintained for 3.5 years based on the average time to return	Full effect maintained for 1 year based on evidence from patients	Full effect maintained for 4 years based on the average time to return

	to an amyloid plaque level of 24.1 CL	who cleared amyloid at 6 months in TRAILBLAZER-ALZ 2 trial	to an amyloid plaque level of 24.1 CL
Post-trial: long-term	Gradual waning over 5 years, assuming residual treatment effect at an amyloid plaque level >24.1 CL	Gradual waning over 2.5 years, aligning with the average time to return to an amyloid plaque level of 24.1 CL	Gradual waning over 9 years, assuming residual treatment effect at an amyloid plaque level >24.1 CL, with no treatment effect remaining at an amyloid plaque level of ~50 CL

However, in acknowledgement of the uncertainty surrounding the long-term treatment effect, long-term gradual waning duration scenarios were conducted where a full treatment effect is maintained for 5.5 years (in line with company base case) with long-term gradual waning at 3, 5, 7 and 11 years.

Table 13: Scenario analyses (revised donanemab PAS price at DGD response) – long-term treatment effect assumptions

Technologies	Inc. costs (£)	Inc. QALYs	ICER (£/QALY)
Revised base case following DGD: full effect maintained for 5.5 years, long-term – gradual waning over 9 years (with no treatment effect remaining at an amyloid plaque level of 49.29 CL)	[redacted]	[redacted]	£12,091
Long-Term: gradual waning duration scenarios			
Scenario: Full effect maintained for 5.5 years, long-term gradual waning over 11 years (with no treatment effect remaining at an amyloid plaque level of 54.89 CL)	[redacted]	[redacted]	£11,556
Scenario: Full effect maintained for 5.5 years, long-term gradual waning over 7 years (with no treatment effect remaining at an amyloid plaque level of 43.69 CL)	[redacted]	[redacted]	£12,871
Scenario: Full effect maintained for 5.5 years, long-term gradual waning over 5 years (with no treatment effect remaining at an amyloid plaque level of 38.09 CL)	[redacted]	[redacted]	£14,057
Scenario: Full effect maintained for 5.5 years, long-term gradual waning over 3 years (with no treatment effect remaining at an amyloid plaque level of 32.49 CL)	[redacted]	[redacted]	£15,955

Abbreviations: ICER: incremental cost-effectiveness ratio; Inc. incremental; PAS: patient access scheme; QALY: quality-adjusted life year.

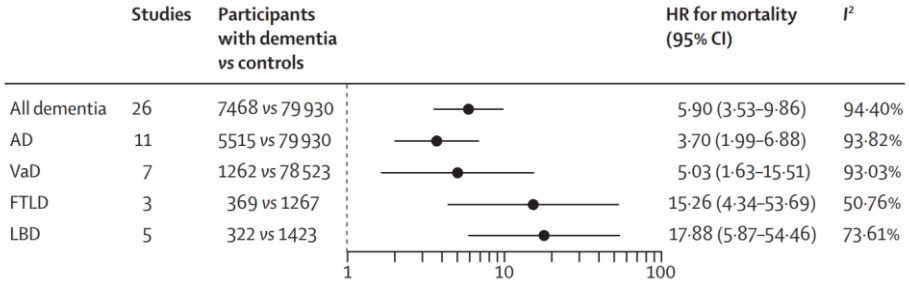
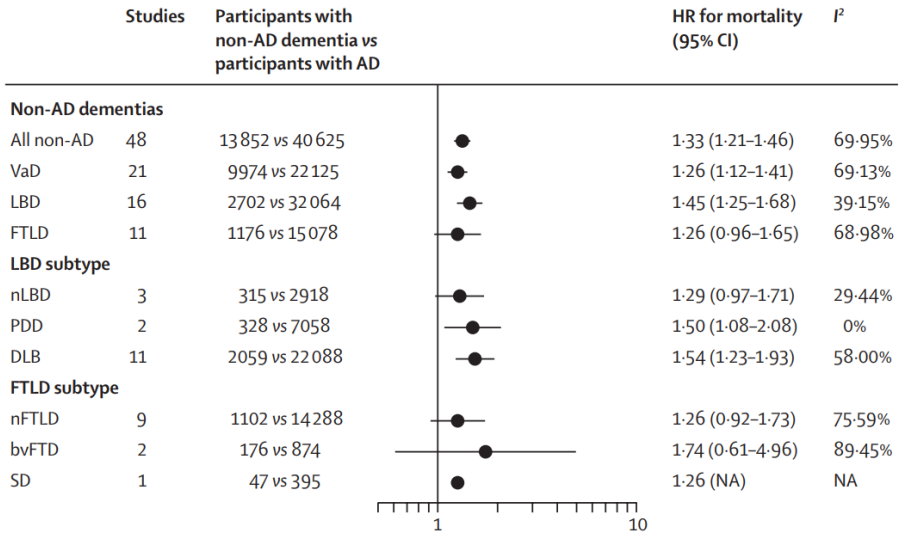
5	**Further information on the source of mortality risk data within the submission** The company acknowledges that mortality risk may differ between the stages of AD dementia and as such, have revised the base case following DGD to include differential mortality risks for the different health states. After discussion at ACM1, the committee concluded that the EAG's approach to modelling mortality, using data from Crowell et al (2023), was more appropriate than the values proposed in the company submission (Table 14).[11] However, the clinical experts noted that they were less certain of how different the mortality risk would be between people with mild or moderated dementia caused by AD. The company NACC analysis utilises the same underlying dataset as the EAG's analysis, however provide a more relevant analysis of the same data, including limiting the population to amyloid positive patients. The company contend that there are several key limitations associated with the Crowell et al analysis: ***Population*** The Crowell et al analysis did not limit to biomarker-confirmed AD patients and it is therefore likely that the sample included patients with other forms of dementia.[12-14] Other forms of dementia have been shown to have a higher mortality risk compared to AD, which means that the EAG analysis would overestimate the mortality risk associated with AD, as demonstrated in Figure 5 and Figure 6 below.[15, 16] The population included within this analysis is therefore less representative of the UK clinical population than the one included within the company NACC analysis and is unlikely to be generalisable. **Figure 5: HR of mortality for people with dementia versus controls**  **Abbreviations:** AD: Alzheimer's disease; FTLD: frontotemporal lobe degeneration; HR: hazard ratio; LBD: Lewy body dementia; VaD: vascular dementia.

Figure 6: HR of mortality for people with non-AD dementia versus AD



Abbreviations: AD: Alzheimer's disease; bvFTD: variant frontotemporal dementia. DLB: dementia with Lewy bodies; FTLD: frontotemporal lobe degeneration; HR: hazard ratio; LBD: Lewy body dementia; NA: not applicable; nFTLD: not specified frontotemporal lobe degeneration; nLBD: not specified Lewy body dementia; PDD: Parkinson's disease dementia; SD: semantic dementia; VVaD: vascular dementia.

Reference group

The mortality risk hazard ratios reported by Crowell et al. use the subset of cognitively normal individuals as the reference cohort, whereas the company NACC analysis considers individuals with MCI due to AD as the reference cohort. As noted in the DGD, published literature suggests that individuals without cognitive impairment are likely to have lower mortality than those with MCI due to AD. This difference in reference cohort means that the Crowell et al hazard ratios are likely to be inflated.

As a consequence of this approach to the reference group, Crowell et al generated a hazard ratio for MCI due to AD of 0.73 (0.55–0.96) which is counter-intuitive as it suggests a survival benefit for patients with MCI due to AD versus the general population. Although the EAG assumed that the

hazard ratio for MCI due to AD was 1 in their base case (Table 14), the Crowell et al hazard ratio for MCI due to AD was not explained, and calls into question the validity of the dataset.

Methodology

Very importantly, in their semiparametric Cox models (compared to the Weibull parametric model used in the company NACC analysis), Crowell et al. censored patients upon progression to the next disease stage, and a new observation segment was generated in the new disease stage (i.e., disease stage was treated as a time-varying covariate). In contrast, the company NACC analysis did not censor patients upon progression to a new stage but continued to follow them until death or administrative censoring. Crowell's analysis is therefore treating death as a competing event, and the HRs obtained from this model represent the relative risk of death for each disease stage, *considering only the survival time within each stage*. Our approach, in contrast considers the cumulative effect of time spent across different stages of the disease spectrum, which is more appropriate to how the HR are implemented within the model, as the hazard ratio is applied to the general population life tables instead of being applied to the transition probability to death.

Table 14: Mortality risk for AD compared to general population

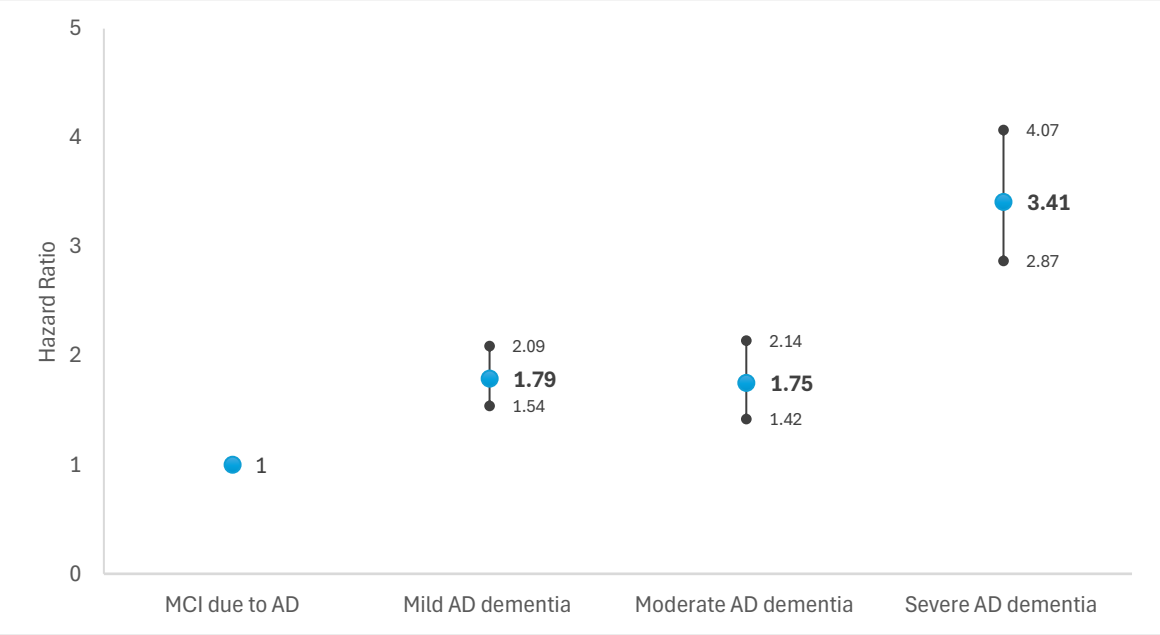
Health State	EAG base case (Crowell et al. 2023)[11]	Company revised base case following DGD (NACC analysis)
MCI due to AD	1**	1
Mild AD dementia	2.4 (1.68. 3.33)	1.79 (1.54, 2.09)*
Moderate AD dementia	3.1 (2.44, 3.94)	1.75 (1.42, 2.14)*
Severe AD dementia	6.6 (4.82, 9.07)	3.41 (2.87, 4.07)

* confidence intervals of HR point estimates overlap
**MCI due to AD HR reported in Supplementary Table 4 of Crowell et al. 2023 of 0.73 (0.55, 0.96), but assumed to be 1 in EAG base case
Abbreviations: AD: Alzheimer's Disease; EAG: External Assessment Group; MCI: mild cognitive impairment; NACC: National Alzheimer's Coordinating Centre.

In light of the detailed explanation outlined above, Lilly requests that the committee reconsiders the conclusion made following ACM1 and instead consider that the company NACC analysis is a more appropriate source of mortality data (Table 14).

Lilly acknowledges that conceptually the lower mortality rate for patients with moderate AD dementia compared to mild AD dementia may lack face validity. Possible reasoning behind this could be due to additional carer support received by patients with moderate AD dementia that patients with mild AD dementia may not receive. However, as shown by Figure 5 below, the numerical difference between these two values is limited to the second decimal place and the confidence intervals of these values overlap considerably, with the upper confidence interval in the moderate AD dementia group being the highest. These values are therefore not statistically different and there is likely no true difference between mild and moderate; this will already be reflected in the company ICERs as they are based on probabilistic modelling. This aligns with the opinion of the clinical experts who expected that there would only be a notable increase in risk of death in those within the severe dementia category.

Figure 7: Mortality risk for AD compared to general population (NACC analysis)



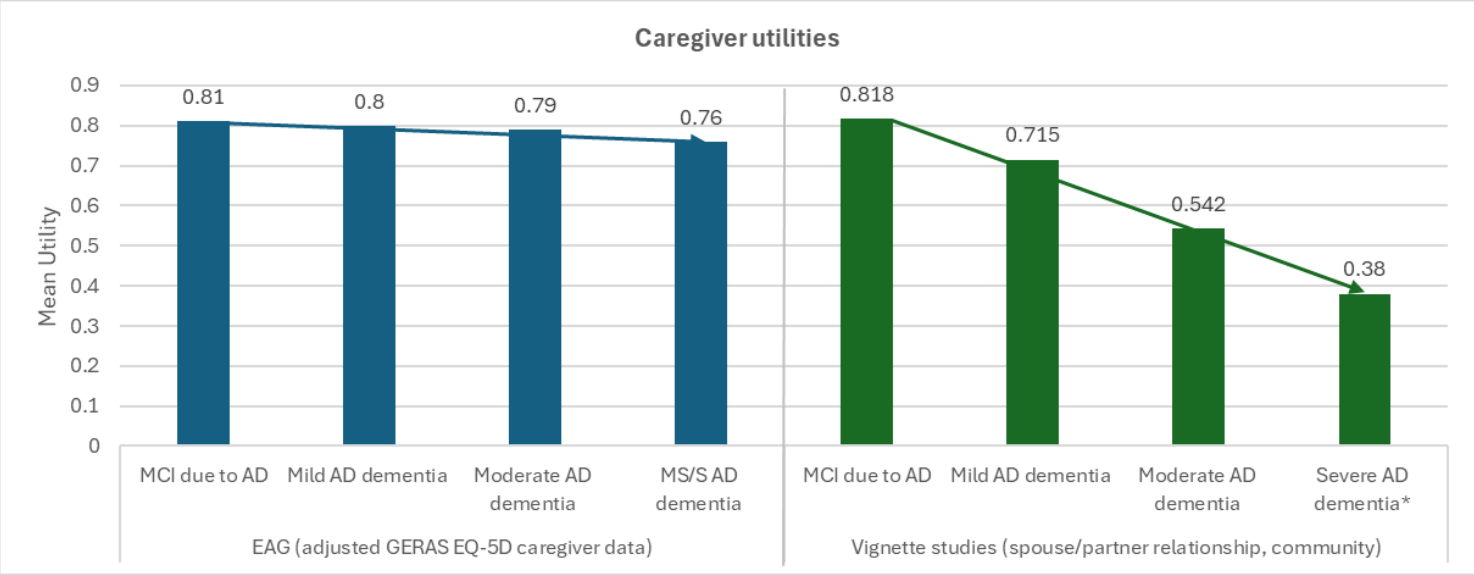
Abbreviations: AD: Alzheimer's disease; MCI: mild cognitive impairment.

6	**Use of proxy EQ-5D utility values** Following ACM1, the committee concluded that the EAG's EuroQoL 5-Dimentions (EQ-5D) utility values obtained from the GERAS study were the estimates most relevant to the UK.[17] The company maintain that use of these data is conservative as the GERAS study was conducted in the community setting and as such, would likely not have captured the more severe cases of AD.[17] This was reflected in the Mini-Mental State Exam (MMSE) definitions used within the study which are higher than seen elsewhere with moderately severe/severe AD severity defined as MMSE <15 where moderate AD is generally defined by an MMSE score between 10–20.[18] These factors suggest that the utility values for patients with severe AD dementia are likely overestimated. The company therefore retains the Landeiro et al. 2020 meta-analysis as the source of utility values in its base case, as these values are more representative of the AD health states in clinical practice.[19] The EAG's assumption that the utility value for people in the MCI caused by AD health state was the same as the general population is also considered plausible and aligned to the company base case. The EQ-5D values from the Landeiro et al. 2020 meta-analysis and the GERAS study were provided via proxy by the carers of patients with mild, moderate or severe dementia. The committee highlighted that the use of proxy values is not in alignment with NICE's manual for health technology evaluations, which states the health-related quality of life (HRQoL) should be measured directly by the patient where possible, noting that there was poor agreement between quality of life estimated by people with AD and by carer proxy. Although the HRQOL was not measured directly in patients in the Landeiro et al. 2020 meta-analysis and in the GERAS study, the proxy EQ-5D values can be considered appropriate. In a previous NICE appraisal for donepezil, galantamine, rivastigmine and memantine for the treatment of Alzheimer's disease (TA217), proxy EQ-5D utility values were accepted by the committee as appropriate.[20] As noted by the committee, it is not possible to measure HRQoL directly from patients at more severe disease states due to cognitive decline, and patient responses may become implausible. The committee raised that there is poor agreement between values reported by people with AD and caregivers, likely due to the aforementioned cognitive decline experienced by people with AD, highlighting the need for a consistent method of obtaining utility values across disease states. The utility values were included within the probabilistic analyses of the company's economic model, and so any uncertainties around these parameters were considered within the model results. Utilising the proxy EQ-5D data for all disease states ensures that there is no uncertainty introduced by the mixing of patient and carer responses. The company notes that there will still be uncertainty introduced by carer proxy, however the use of the EQ-5D via proxy has been shown to correlate with MMSE scores in patients in different stages of Alzheimer's disease.[21] This study also highlighted the difficulty in patients with mild to

	moderate cognitive impairment in completing the EQ-5D questionnaire, as patients may have difficulty understanding the questions in the quality of life (QoL) instruments. Within this study it was noted that patients gave higher ratings on all instruments for all disease state than carers, and so the results were partially due to low response rates in more severe disease states.[21] The company also notes that variation in the utility values was included within the company's probabilistic cost-effectiveness model in order to address uncertainty around these parameters.
7	**Further information about the approach to deriving carer utilities** **Evidence demonstrating that EQ-5D is not appropriate**: The company maintains that EQ-5D is not an appropriate measure to estimate utilities associated with being a carer for patients with MCI due to AD or mild AD dementia. The EQ-5D was designed to quantify an individual's overall health status and as such, the five dimensions have limited relevance to caregiver utility. As part of the vignette studies, focus groups were conducted with caregivers of people with MCI and dementia associated with Alzheimer's disease. The most common areas of impact reported by these caregivers included uncertainty regarding whether their loved one can understand or remember things, work-related impact, the loss of time to themselves, irritation/frustration, having to learn how to perform tasks for which they were previously not responsible and having to handle all the driving. These insights highlight the limited overlap between the EQ-5D and the most important aspects of caregiver impact, demonstrating the lack of content validity of the EQ-5D in this circumstance. Published literature also supports that the EQ-5D is an inadequate tool for assessing the utility of caregivers of Alzheimer's disease patients. A study by Reed et al (2017) of 1495 caregivers suggests that the EQ-5D is not particularly effective at capturing the true impact on caregivers of caring for patients with AD dementia: 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.[22] EQ-5D index demonstrated a weak correlation with perceived caregiver burden and measure of caregiver time. [22] Similar limitations were identified with the EQ-5D-5L by Sokolova et al (2024),[23] which exhibited a ceiling effect and failed to differentiate between caregivers of patients with moderate and severe Alzheimer's, thus restricting its effectiveness in detecting differences across health states. Building on the acknowledged limitations of the EQ-5D in assessing caregiver utilities, the Spillovers in Health Economic Evaluation and Research (SHEER) task force highlighted the absence of suitable tools for evaluating caregiver spillover effects in health economic analyses. Their recent recommendations emphasised the need for developing novel preference-based measures specifically designed to capture these health spillovers due to the lack of empirical evidence supporting any existing instruments.[24] Echoing these concerns, a publication from the EuroQol Group recognised that the EQ-5D falls short in accurately reflecting the impact of a patient's health on their carers.

	Due to the preponderance of evidence suggesting that the EQ-5D is not appropriate for assessing the burden of caring for a family member with MCI or AD dementia, Lilly maintains that the vignette-based studies are a more appropriate method to estimate carer utility. As such, the EAG's base case approach utilising EQ-5D data from the GERAS study cannot be considered an appropriate source of utility data for carers within the model. As highlighted in Comment 6, use of these data can be considered overly conservative as the GERAS study was conducted in the community setting and would likely not have captured the more severe cases of AD.[17] MMSE definitions used within the study were higher than seen elsewhere with moderately severe/severe AD severity defined as MMSE <15 where moderate AD is generally defined by an MMSE score between 10–20.[18] These factors suggest that the utility values for the carers of patients with severe AD dementia are likely overestimated. This is further exemplified by the lack of face validity in the utility values. Firstly, there are limited differences in utility values for caregivers of patients across the three stages of AD dementia, with a range of only 0.04 (Figure 8). Secondly, the EAG had to adjust the data in the model by assuming that caregivers of patients with mild AD dementia had the same quality of life as the general population, based on age and gender distribution within the economic model, as the EQ-5D estimates for caregivers of mild AD dementia patients were higher than the general population. Additionally, the median value for all health states for the EQ-5D caregiver utility is 0.89 which is above the general population value.[25]

Figure 8: Caregiver utility values across the health states



*adjusted based on the delta between the moderate health states from the 2 vignette studies.
Abbreviations: AD: Alzheimer's Disease; EAG: External Assessment Group; MCI: mild cognitive impairment.

Consideration of other generic preference-based measures and condition-specific measures: While the EQ-5D has received the most attention in the literature, other generic and condition-specific instruments designed to yield utilities also focus on an individual's health often without consideration of caregiver impact. Therefore, the available generic and condition-specific utility measures are likely to have the same limitations, and they are unlikely to be sensitive to the impact of caring for a close relative with MCI or dementia associated with Alzheimer's disease.

Use of vignette studies: As demonstrated above, EQ-5D and other generic measures are not considered appropriate to measure changes in carer utility. As such, carer utilities were derived from two vignette studies conducted by Lilly based on a time trade-off approach; as is recommended by NICE for situations in which use of EQ-5D is not appropriate.[26-29]

The structure of the carer utility values applied in the model was also discussed within ACM1. Lilly maintains that splitting utility by type of caregiver (spouse or child caregivers), rather than by residential status (living with or not living with) as suggested by the EAG, is appropriate. By exclusively using the residential status approach, the emotional impact of caring for someone with AD, particularly on child caregivers, is not accounted for within the analysis. The lack of face validity of this approach can clearly be seen within the EAG's scenario analysis, where the HRQoL of a child caregiver for a patient living within the community is assumed to be the same as for a patient living within residential care. This overlooks key aspects of caring for someone in the community who does not have constant care, such as the decreased availability of specialised resources (e.g., staff, medical equipment), greater stress about the wellbeing of the patient and increased time spent caring for the patient. Lilly therefore have not updated the base case assumptions regarding carer utility and utility values applied within the model are presented in Table 32 of Document B of the original company submission.

Lilly has also run a scenario to include utility values for carers living with patients (previously spouse carers in the community) and carers not living with patients (previously child carers in the community and all carers in residential settings), as per the EAG's scenario analysis. The utility values used in the scenario analysis model are summarised in Table 15 and the results of the scenario analysis are presented in Table 16.

Table 15: Carer utility values within the model (replicated from the EAG scenario analysis)

Health state	Living with Patient	Not living with patient
MCI due to AD	0.82	0.84
Mild AD dementia	0.79	0.74
Moderate AD dementia	0.65	0.71
Severe AD dementia	0.49	0.64

Abbreviations: AD: Alzheimer's Disease; EAG: External Assessment Group.

Table 16: Scenario analyses (revised donanemab PAS price at DGD response) – source of carer utility values

Technologies	Inc. costs (£)	Inc. QALYs	ICER (£/QALY)
Revised base case following DGD: Vignette study (Belger et al. 2022 and Matza et al. 2024)	[redacted]	[redacted]	£12,091

	Scenario: EAG use of vignette study | [redacted] | [redacted] | £13,476

Abbreviations: ICER: incremental cost-effectiveness ratio; Inc. incremental; PAS: patient access scheme; QALY: quality-adjusted life year.

Number of caregivers per patient: Lilly notes the committee's concern that there is a lack of published evidence on the utilities for secondary carers of patients with AD and acknowledges that the disutility impact may differ between primary and secondary carers. However, the EAG's approach of only applying carer utility values for 1 carer underestimates the impact of AD and treatment with donanemab on caregiver quality of life. The 1.8 value used within the company submission was based on data from the GERAS EU study (mean number of caregivers participating in caring for the patient in the pooled cohort (n=1,497) as well as in the individual UK cohort [N=526] was 1.8 [SD: 1.1]).[30] Although Lilly accepts that the burden on secondary carers may be different to that of primary carers, it is reasonable to expect that this burden will be greater than zero and as such, consider the EAG's approach to be overly conservative.

To test the importance of this assumption on decision-making, scenario analyses have been conducted investigating applying different values for the number of caregivers to the carer utility value input, and the results are presented in Table 17. Reducing the number of carers per patient increases the ICER with an assumption of 1.2 carers associated with an ICER of £14,073 compared to £12,091 when assuming 1.8 carers per patient, as indicated by the GERAS study.

Table 17: Scenario analyses (revised donanemab PAS price at DGD response) – number of carers

Technologies	Inc. costs (£)	Inc. QALYs	ICER (£/QALY)
Revised base case following DGD: 1.8 carers per patient	[redacted]	[redacted]	£12,091
1.6 carers per patient	[redacted]	[redacted]	£12,687
1.4 carers per patient	[redacted]	[redacted]	£13,344
1.2 carers per patient	[redacted]	[redacted]	£14,073

Abbreviations: ICER: incremental cost-effectiveness ratio; Inc. incremental; PAS: patient access scheme; QALY: quality-adjusted life year.

8	**Further information on the anticipated infusion cost associated with treatment with donanemab** Lilly acknowledges that there is a significant difference between the estimated infusion cost included within the company submission and the EAG base case (£207.59; 2021/22 reference costs: SB12Z) and that included in the NHS England model (£565; WD02Z cost uplifted). However, Lilly

	strongly maintains that the cost originally included within both the company and the EAG model base case is the appropriate cost to include and that the NHS England estimate represents a considerable overestimation of the administration costs. The administration costs included within the company submission is the reference cost associated with delivering simple parenteral chemotherapy at first attendance. While Lilly acknowledges that there may be differences between administering chemotherapy and administering donanemab, this use of this reference cost may well be an overestimation of the infusion costs as opposed to an underestimation. Administration of chemotherapy requires both aseptic technique and specialised handling of the cytotoxic chemotherapy substances. However, administration of donanemab requires aseptic technique only for the dilution of the vial contents into the saline infusion bag and can be performed by a wider range of staff in a wider range of settings. Donanemab does not need to be prepared by hospital pharmacies and can instead be drawn up in infusion suites by nursing staff, this was supported by clinical experts at the second lecanemab committee meeting who noted that the hospital pharmacy were not involved within the clinical trial as infusion was too simple. Conversely, the NHS England cost estimate is based on the national tariff for an AD or dementia patient day-case attendance treated by a non-specialist mental health service provider, a cost which has no relevance whatsoever to the administration of a simple parenteral infusion. To note, the cost quoted by NHS England has since been withdrawn from the reference costs as it goes against the NHS' policy on the treatment of mental health patients.[31] Therefore, although this is a disease-specific code, it assumes that the infusion of donanemab will require a full day of mental health treatment by a non-specialist. Within the SmPC, it is specified that donanemab should be administered over at least 30 minutes with patients observed for 30 minutes post-infusion.[32] As such, the assumption by NHS England significantly overestimates the required resource needed for donanemab infusion. Lilly note that NHS England have since updated their proposal, as was presented in the second committee meeting for lecanemab. NHS England have now proposed an infusion cost of £432, which was based on the cost associated with infusion of COVID mAbs in previous NHS England modelling. However, in TA971 (MTA for therapeutics for people with COVID-19), the EAG preferred to use the SB12Z infusion cost, in line with the company's base case.[33] Additionally, COVID mAbs are only prescribed for acutely unwell patients who likely require respiratory or oxygen support within an inpatient setting, it is also likely that these patients are immunocompromised or have significant comorbidities. This is in stark contrast to an otherwise well patient who presents for a routine 30 min infusion in an outpatient setting, as would be the case for administration of donanemab. Lilly therefore consider that costs associated with mAb infusion in other chronic disease settings are a more appropriate proxy such as ulcerative colitis. In the NICE evaluations for risankizumab (TA998),[34] ustekinumab (TA633),[35] filgotinib (TA792),[36] ozanimod (TA828)[37] and mirikizumab

(TA925),[38] the costs for IV administration were calculated as the average of a consultant (£182.93) and a non-consultant led (£87.78), non-admitted, face-to-face, follow-up appointments (code WF01A) in gastroenterology. Within the most recent appraisal (risankizumab; TA998), the unit costs were taken from the 2021/2022 NHS Reference Costs, and the cost per IV administration was estimated to be £135.36.[34] In line with this approach, Lilly have conducted a scenario in which the cost of infusion is based on the cost of neurology consultant-Led (first attendance) outpatient attendance (£222.91). In a further scenario, Lilly have used the SB13Z infusion cost taken from the 2021/2022 NHS Reference Costs, which refers to the delivery of complex parenteral chemotherapy. The results of these scenario analyses demonstrate that the use of the alternate infusion costs has a minimal impact on the cost-effectiveness results.

Table 18: Scenario analyses (revised donanemab PAS price at DGD response) – IV infusion cost

Technologies	Inc. costs (£)	Inc. QALYs	ICER (£/QALY)
Revised base case following DGD: SB12Z Deliver of Simple Parenteral Chemotherapy (£207.59)	[redacted]	[redacted]	£12,091
Scenario: Neurology Consultant-Led (first attendance) Outpatient Attendance (£222.91)	[redacted]	[redacted]	£12,368
Scenario: SB13Z Deliver of Complex Parenteral Chemotherapy (£256.95)	[redacted]	[redacted]	£12,984

Abbreviations: ICER: incremental cost-effectiveness ratio; Inc. incremental; IV: intravenous; PAS: patient access scheme; QALY: quality-adjusted life year.

9

Disaggregated results for individual health states

The committee has requested disaggregated, discounted and undiscounted model results for the individual health states in the revised base case following DGD. These are presented in Table 19, Table 20 and Table 21.

Table 19: Summary of QALY gain by health

Health state	QALY intervention (donanemab)	QALY comparator (BSC)	Increment	Absolute increment	% absolute increment
Community Setting					
MCI due to AD*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Mild AD dementia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Moderate AD dementia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Severe AD dementia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Residential Care					
MCI due to AD*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mild AD dementia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Moderate AD dementia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Severe AD dementia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AD: Alzheimer's Disease; BSC: best supportive care; MCI: mild cognitive impairment; QALY: quality-adjusted life year.

Table 20: Summary of health state costs by health state

Health state	Cost intervention (donanemab)	Cost comparator (BSC)	Increment	Absolute increment	% absolute increment
MCI due to AD*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mild AD dementia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Moderate AD dementia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Severe AD dementia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AD: Alzheimer's Disease; BSC: best supportive care; MCI: mild cognitive impairment.

Table 21: Summary of predicted resource use by category of cost

Item	Cost intervention (donanemab)	Cost comparator (BSC)	Increment	Absolute increment	% absolute increment
Acquisition Costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Administration and Related Costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Diagnostic Testing Costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Amyloid Monitoring Detection Costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ARIA Adverse Events Costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Non-ARIA Adverse Events Costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Disease Management Costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Concomitant Medication Costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ARIA: amyloid-related imaging abnormality; BSC: best supportive care.

10

Update to the proportion of patients starting in the MCI due to AD and mild AD dementia health states

Given the stopping rule detailed in the marketing authorisation that states that patients should stop treatment with donanemab once they reach moderate AD dementia, Lilly considers it necessary to update the proportion of patients starting in the MCI due to AD and mild dementia due to AD health states in the model. Within the original company submission, the proportions were informed by the proportion of MCI due to AD and mild dementia due to AD patients in the TRAILBLAZER-ALZ 2 trial (20.4% in MCI due to AD and 79.6% in mild AD dementia). However, clinical expert opinion suggests that given the stopping rule at moderate, clinicians would be more likely to initiate treatment with donanemab earlier in the disease and less likely to risk initiating in the later stages of mild AD to avoid the risk of having to apply the stopping rule, which patients and their families

would find distressing and ensure that, as far as possible, patients would be able to receive the full course of donanemab. Additionally, within the recent lecanemab appraisal, the EAG estimated that 38% of patients would initiate in MCI due to AD and 62% in mild AD dementia.[39]

Real world experience data indicated that the proportion of patients initiating disease-modifying treatment in the MCI health state may be higher than the lecanemab EAG's estimate. A recent retrospective observational study of 71 patients who were treated with lecanemab reported that 35 (49.3%) patients were considered MCI due to AD and 36 (50.7%) were considered mild AD dementia.[40] Other RWE research suggests that the proportion of patients with MCI due to AD initiating lecanemab in clinical practice ranges from 60.8% to 79%, indicating that the proportion of patients originally proposed within the company submission is not an accurate assumption according to the latest data. Most recently, Kile et al published RWE that found 70% of the 234 patients who initiated lecanemab had MCI due to AD and 30% had mild AD dementia.[41] The base case has therefore been updated to reflect the proportions published in Kile et al (2024), with scenario analyses run to investigate the impact of using Shields et al (2024) and the EAG's estimate from the lecanemab appraisal (Table 22).

Table 22: Scenario analyses (revised donanemab PAS price at DGD response) – proportion of patients starting in the MCI due to AD and mild AD dementia health states

Technologies	Inc. costs (£)	Inc. QALYs	ICER (£/QALY)
Revised base case following DGD: 70% MCI due to AD / 30% mild AD dementia – Kile et al. 2024	[redacted]	[redacted]	£12,091
Scenario: 49.3% MCI due to AD / 50.7% mild AD dementia	[redacted]	[redacted]	£16,445
Scenario: 38% MCI due to AD/ 62% mild AD dementia (based on the lecanemab appraisal)	[redacted]	[redacted]	£19,119

Abbreviations: ICER: incremental cost-effectiveness ratio; Inc. incremental; PAS: patient access scheme; QALY: quality-adjusted life year.

11

Proportion of patients transitioning to residential care annually

The committee reported preference for the EAG's source for annual risk of residential care, the European GERAS study, citing this to be more suitable due to the inclusion of UK patients and that a higher rate of residential care was estimated for people with severe dementia caused by AD. The company acknowledges that the European GERAS study is suitable and accept the values for annual risk of residential care to be included in the base case.

12

Inclusion of informal / unpaid carer costs in the base case

Lilly acknowledges 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.[28, 42] As detailed in the company submission, informal or unpaid care accounts for 40% of total dementia care costs and is estimated to total £18.2 billion in 2025.[43] This demonstrates the significant burden associated with informal care in the UK and highlights the need to broaden the perspective of the cost-effectiveness analysis. This issue was highlighted within Issue 8 of the NICE HTA Lab report, which **invited** non-reference case analyses and suggested that it may be appropriate to consider the cost of the time of providing this care, even when adopting an NHS or PSS perspective.[44] Additionally, Section 4.4.24 of the NICE manual states that *'when care by family members, friends or a partner might otherwise have 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*'.[28] As such, Lilly maintains that the PSSRU report is the most appropriate source of health resource utilisation costs and have not made any changes within the base case analysis.

Table 23: Scenario analyses (revised donanemab PAS price at DGD response) – informal care costs

Technologies	Inc. costs (£)	Inc. QALYs	ICER (£/QALY)
Revised base case following DGD: Including informal care costs	[redacted]	[redacted]	£12,091
Excluding informal care costs	[redacted]	[redacted]	£21,357

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

13

Sensitivity analysis to reduce risk of bias in TRAILBLAZER ALZ-2 trial

In response to the committee's concerns about potential risk of bias in the TRAILBLAZER ALZ-2 trial results due to possible study unblinding because of the occurrence of amyloid-related imaging abnormalities (ARIA) events, Lilly has conducted a sensitivity analysis in which patients who had ARIA or IRR events were censored to reduce the possible risk of bias. The sensitivity analysis demonstrates that there are no significant differences in results when patients with ARIA/IRR were censored and as such, the risk of bias within the results is low. The same conclusion can be drawn when looking at the results from NCS2 and MMRM model presented in Comment 2.

Table 24: Hazard ratios of disease progression for donanemab versus BSC (CDR-SB scale and iADRS scale)

	CDR-SB HR (95% CI) vs BSC	iADRS HR (95% CI) vs BSC

	UK eligible population in TRAILBLAZER-ALZ 2	[redacted]	[redacted]
	Meta-analysis of TRAILBLAZER-ALZ 2 and TRAILBLAZER-ALZ on the UK eligible population	[redacted]	[redacted]
	Meta-analysis of TRAILBLAZER-ALZ 2 and TRAILBLAZER-ALZ censoring patients at their first occurrence of ARIA/IRR on the UK eligible population	[redacted]	[redacted]
	Abbreviations: ARIA: amyloid-related imaging abnormalities; BSC: best supportive care; CDR-SB: Clinical Dementia Rating Scale – Sum of Boxes; iADRS: Integrated Alzheimer Disease Rating Scale; CI: confidence interval; HR: hazard ratio; IRR: infusion-related reactions.		
14	**Factual inaccuracies noted in the Draft Guidance Document** Within the Draft Guidance Document, committee point 3.13 states the following: *'The company noted that in TRAILBLAZER-ALZ 2, amyloid clearance (see section 3.14) was seen in 29.7% of people who had amyloid-PET screening at 6 months and **36.4% of people who had amyloid-PET screening at 12 months**.'* This is a misinterpretation of the company's data. These values refer to the percentage of screened patients who reach amyloid clearance (<24.1 CL) at each timepoint, rather than the cumulative percentage of patients who reach amyloid clearance, as the committee's wording suggests. As outlined in the company's response to Clarification Question B14, 29.7% of patients had achieved amyloid clearance at 6 months, and **66.1% at 12 months**. This equates to an *additional* 36.4% patients achieving clearance at 12 months.		
15	**Updates to managed access proposal** Some uncertainties identified by NICE throughout the appraisal could be resolved via managed access with a period of data collection. Lilly are working to update the original managed access proposal following the feedback received during the first committee meeting and within the draft guidance document, and will submit this to NICE in due course.		

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 Wednesday 20 November. Please submit via NICE Docs.

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.
- 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 '[redacted]' in turquoise, and all information submitted as '[redacted]' 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 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.

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 Wednesday 20 November. Please submit via NICE Docs.

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

Lilly Response to Additional Information Request

Please provide the analysis to support the assumed amyloid reaccumulation rate of 2.8 CL/year based on 4 trials (company submission [CS] pg 74). We note that:

- Shcherbinin et al 2023 (CS reference 160 and draft guidance [DG] response reference 4) is an abstract that gives an amyloid re-accumulation rate of 3.4 CL/year based on an analysis of 46 participants from 2 trials: TRAILBLAZER-ALZ and AACD. Please provide the slides/poster conference presentation for this abstract, which is described to include data from a third trial: TRAILBLAZER-EXT.

Please see Scherbenin (2023) AAIC presentation attached to this response, where slide 12 shows the key analysis in which 2023 patients were studies from 4 clinical trials (AACD PK/PD study, TB-ALZ, TB-ALZ-EXT, and TB-ALZ 2) were assessed and the average predicted rate of amyloid plaque re-accumulation is ~2.8 CL/year.

- Please provide CS reference 161, which is missing from the reference pack (Evans C CM, Shcherbinin S. Donanemab TRAILBLAZER-EXT: Longer-term Effects on Brain Amyloid and Tau deposition. Blood-based Biomarkers, and Clinical Progression of Alzheimer Disease, In International Conference on Alzheimer's and Parkinson's Disease (AD/PD), Gothenburg, Sweden, 2023.) Please provide the abstract and full conference presentation.

Please find the Evans (2023) AD/PD TRAILBLAZER-EXT presentation attached to this response.

- Please clarify which 4 trials are included in the amyloid reaccumulation rate analysis, including the number of people included in this analysis, and the time frames over which amyloid reaccumulation was measured in each of these trials.

This is outlined in response to Q1 and within the Scherbenin (2023) AAIC presentation.

- In the DG response, reaccumulation of amyloid is assumed to be linear over time. Please provide evidence that justifies this assumption.

This is an assumption in line with Figure 1B of the Jagust et al. (2021) paper which shows that the relationship between time and amyloid accumulation is sigmoidal, though over the period of interest (~12.85cL to ~50cL) it appears visually to be linear.

Please provide the analysis showing that for the marketing authorisation population, the time taken for a return to an amyloid plaque level >24.1 CL, which equates to amyloid positivity, after last treatment is 4 years.

For the marketing authorisation population, the mean amyloid plaque level at 18 months was 12.89cL (t_rm_amy1_exc_e4e4_anitco). Therefore, re-accumulation of amyloid plaque at 2.8cL means that it would take 4 years to reach 24.09cL. It would then take a further 9 years to reach 49.29cL. These calculations informed our medium- and long-term treatment effect waning assumptions.

Finally, following our earlier query about when data will be available from the long-term extension studies, please clarify what data is available from the long-term extension of TRAILBLAZER-ALZ including to provide any supportive clinical data.

Please find the Evans (2023) AD/PD TRAILBLAZER-EXT presentation attached to this response.

Donanemab TRAILBLAZER-EXT: Longer-term Effects on Brain Amyloid and Tau Deposition, Blood-based Biomarkers, and Clinical Progression of Alzheimer's Disease

Cynthia D. Evans, Michael Case, Sergey Shcherbinin, Jiangang Jameson Cai, Ian Kennedy, Serap Nery, Alette Wessels, Emily C. Collins, Dawn A. Brooks, John R. Sims

Eli Lilly and Company, Indianapolis, IN, USA

International Conference on Alzheimer's and Parkinson's Diseases (AD/PD)
Gothenburg, Sweden
March 28 – April 1, 2023

Scan the QR code or use this URL
https://lillyscience.lilly.com/congress/adpd2023
for a list of all Lilly content presented at the congress

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Disclosures

- Cynthia Evans is an employee of Eli Lilly and Company.
- Amyvid (Florbetapir F 18) was developed at Avid Radiopharmaceuticals and is marketed by Eli Lilly and Company as a radioactive diagnostic agent for Positron Emission Tomography (PET) imaging of the brain to estimate β-amyloid neuritic plaque density; safety and effectiveness of Amyvid (Florbetapir F 18) has not been established for predicting development of dementia or other neurologic conditions and monitoring responses to therapies.
- Tauvid (Flortaucipir F 18) is approved for use in the US with PET imaging of the brain to estimate the density and distribution of aggregated tau neurofibrillary tangles in adult patients with cognitive impairment who are being evaluated for Alzheimer's disease.
- All discussions refer to investigational purposes only.

TRAILBLAZER-EXT Overview

TRAILBLAZER-EXT (NCT04640077) is a Phase 2 donanemab long term follow-on study in which TRAILBLAZER-ALZ participants originally randomized to placebo receive donanemab, and participants originally randomized to donanemab participated in a long-term follow-up visit with no treatment.

Study Population

- Participated in TRAILBLAZER-ALZ trial
- No current serious or unstable illnesses
- Have a study partner
- Have not received treatment with a passive amyloid targeting therapy after completion of originating study
- Stable symptomatic AD medications at least 30 days prior to Part A

Presentation Objectives

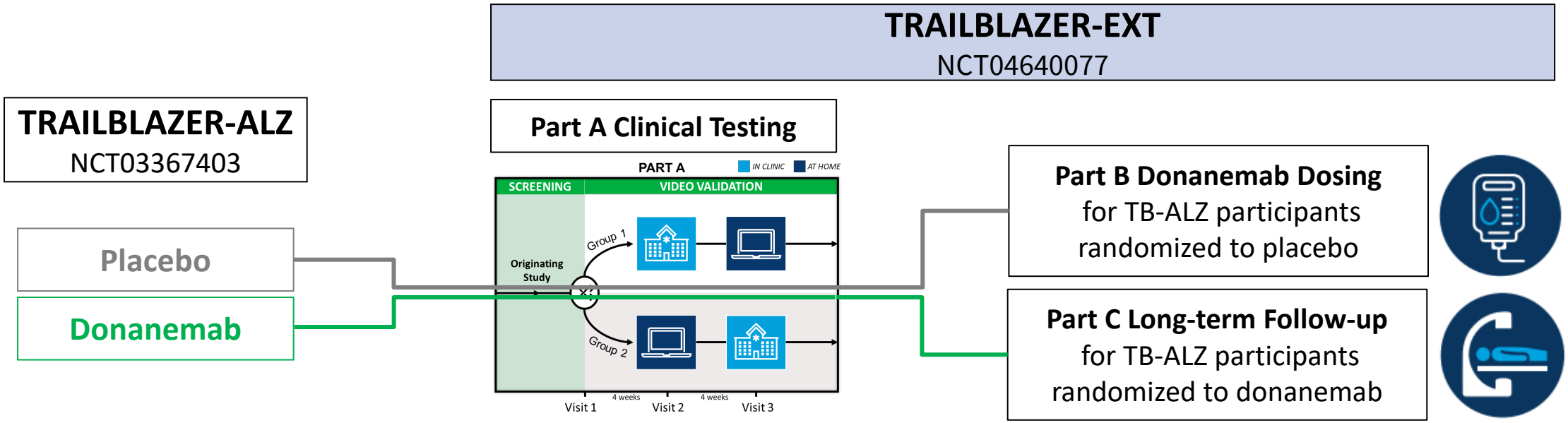
To examine longer term effects of prior donanemab treatment on

- amyloid lowering & reaccumulation
- clinical changes
- accumulation of aggregated tau and plasma phospho-tau

TRAILBLAZER-EXT Objectives & Study Design

TRAILBLAZER-EXT study objectives:

Part A: evaluate the reliability of video teleconference compared with on-site administered cognitive & functional measures
Part B: evaluate safety and tolerability of donanemab in participants randomized to placebo in TB-ALZ
Part C: assess long term effects of donanemab on brain amyloid deposition and progression of AD following prior treatment with donanemab



Results presented by Langbaum *et al.* CTAD 2022

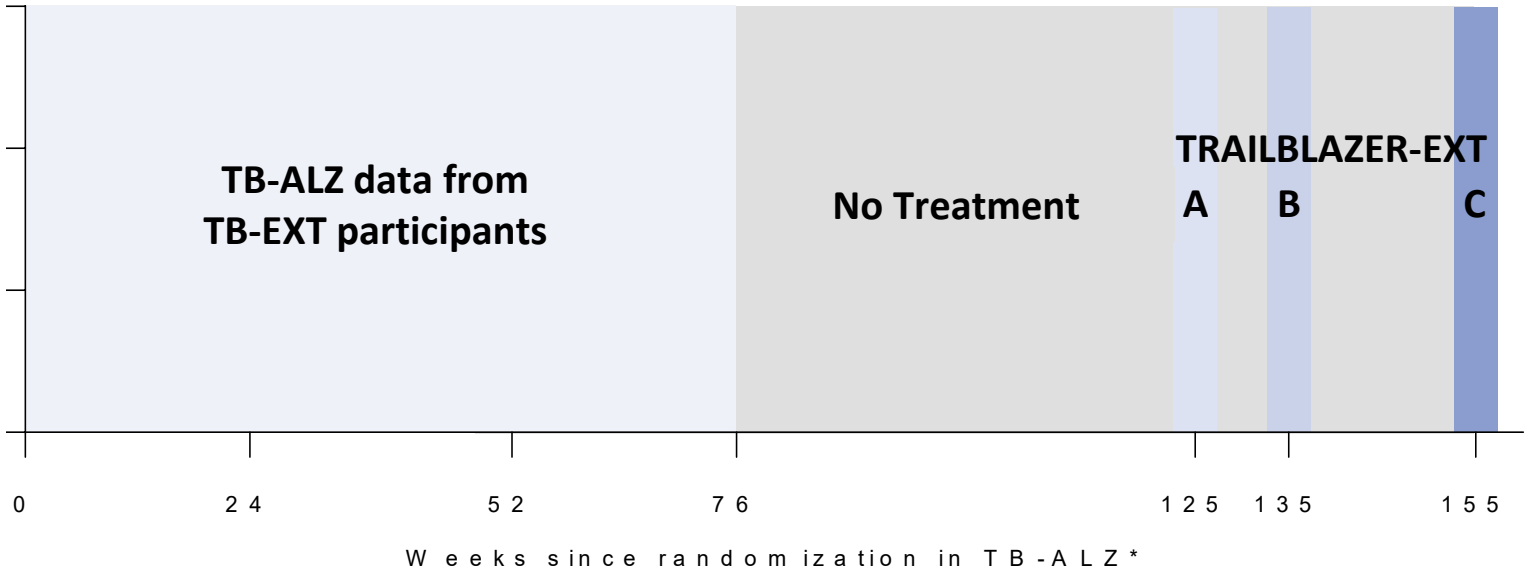
TRAILBLAZER-EXT Analysis Populations

TRAILBLAZER-ALZ

TRAILBLAZER-EXT

Placebo n = 126	n=58	**Part A Clinical Testing** First onsite visit iADRS, CDR-SB	n=43	**Part B** Plasma P-tau217 before donanemab dosing
Donanemab n = 131	**n=25**		**n=17**	**Part C Long-term Follow-up** Amyloid & Tau PET, P-tau217

n = number of participants contributing data to analyses



*TRAILBLAZER-EXT weeks since randomization are ~means. Range: Part A 82-159, Part B 96-200, Part C 124-211

TB-EXT Participant Baseline Demographics at the Beginning of TB-ALZ

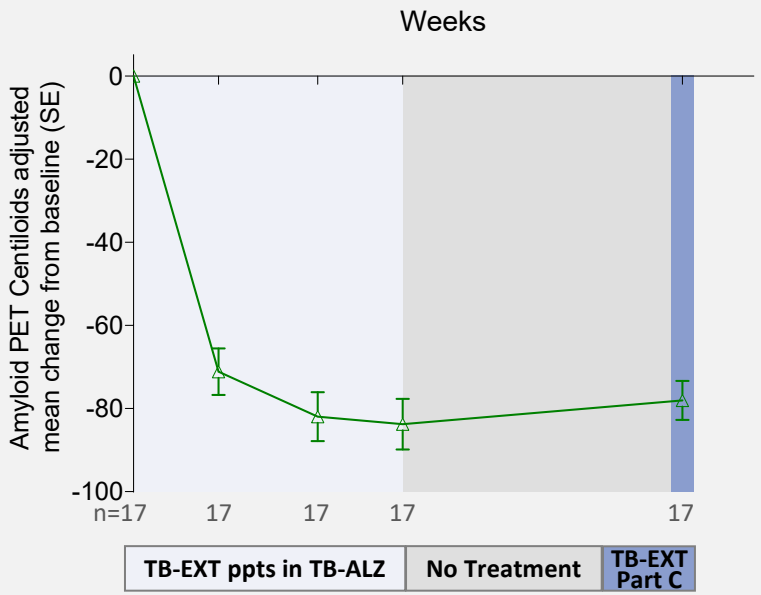
Demographic	Placebo N=58	Donanemab N=25
Female, n (%)	32 (55)	13 (52)
Age, mean (SD)	75.5 (5.4)	74.2 (5.9)
Education 13+ years, n (%)	42 (72)	17 (68)
***APOE* ε4 carrier, n (%)**	41 (71)	21 (84)
ε2/ε3	1 (2)	1 (4.0)
ε2/ε4	2 (3)	1 (4.0)
ε3/ε3	16 (28)	3 (12)
ε3/ε4	28 (48)	15(60)
ε4/ε4	11 (19)	5 (20)
AChEI and/or Memantine use, n (%)	37 (64)	19 (76)

Scale/biomarker, mean (SD)	Placebo N=58	Donanemab N=25
ADAS-Cog$_{13}$	26.8 (7.5)	24.4 (6.8)
ADCS-ADL	68.6 (7.6)	70.2 (5.7)
ADCS-iADL	50.0 (6.9)	51.4 (5.4)
iADRS	108.2 (12.6)	112.0 (8.9)
MMSE	23.8 (3.1)	24.6 (2.8)
CDR-SB	3.1 (1.5)	3.2 (1.7)
Amyloid level, CL	104 (29)	111 (40)
AD signature-weighted neocortical tau PET SUVR	1.20 (0.12)	1.21 (0.12)

Demographics of TB-EXT Part A participants upon entering TB-ALZ. AChEI = acetylcholinesterase inhibitor; ADAS-Cog$_{13}$ = Alzheimer's Disease Assessment Scale - Cognitive subscale; ADCS-(i)ADL = Alzheimer's Disease Cooperative Study-(instrumental) Activities of Daily Living Inventory; APOE 4 = Apolipoprotein E allele 4; CDR-SB = Clinical Dementia Rating Scale Sum of Boxes; CL = Centiloid units; iADRS = Integrated Alzheimer's Disease Rating Scale; MMSE = Mini–Mental State Examination; PET = positron emission tomography; SD = standard deviation; SUVR = standardized uptake value ratio

TRAILBLAZER-EXT: Examining Amyloid Plaque Reaccumulation

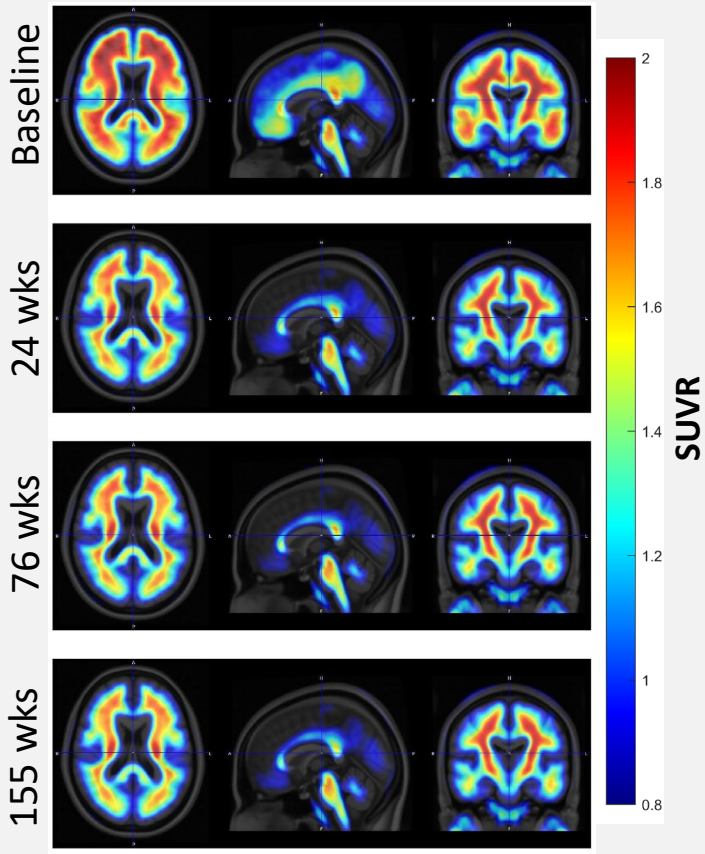
Amyloid Plaque Level on Florbetapir PET



Mean annualized reaccumulation rate 4.0 ± 2.0 CL/yr (LS mean ± SE)

TB-EXT Part C participants' baseline TB-ALZ amyloid PET reduced from 109 to 26 CL in 76 weeks (76% decrease from baseline), then increased to mean of 31 CL ~79 weeks later (72% decrease from baseline).

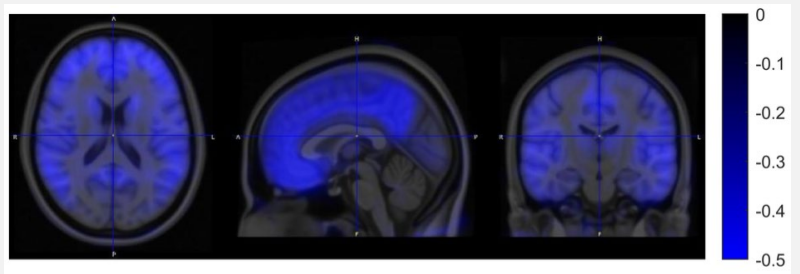
Florbetapir PET SUVR Images



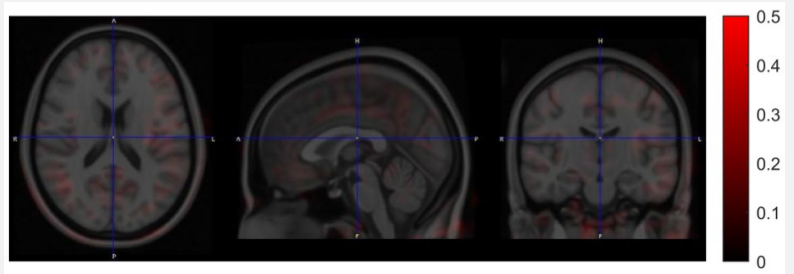
High spatial similarity between 24-, 76- & 155-week average florbetapir SUVR images among n=17 TB-EXT Part C participants

Marked Reduction in Amyloid & Minimal Reaccumulation

Amyloid reduction in TB-ALZ
76 weeks - baseline



Amyloid accumulation in TB-EXT part C
155 weeks – 76 weeks



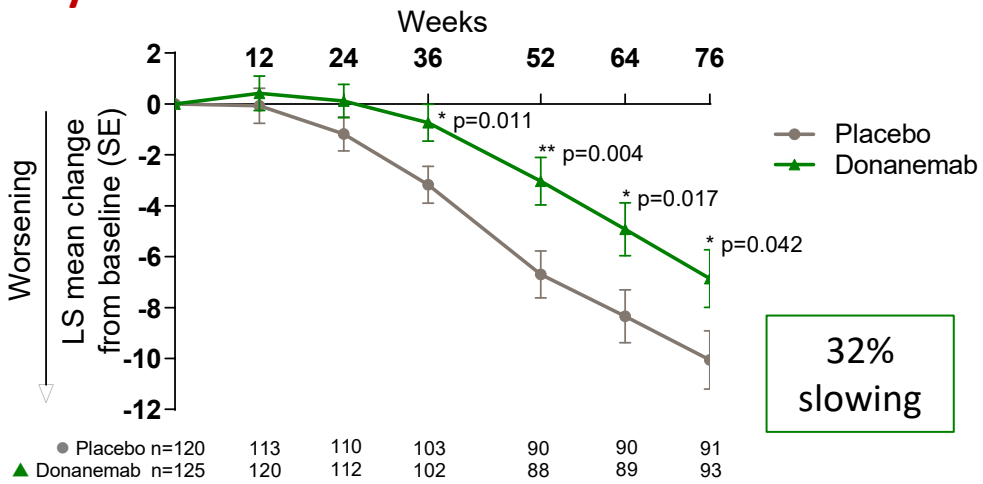
Average change in SUVR among n=17 TB-EXT Part C participants (whole cerebellum as a reference)

TRAILBLAZER-ALZ: Donanemab Slowed Cognitive & Functional Decline on all Clinical Endpoints Compared with Placebo

TRAILBLAZER-ALZ

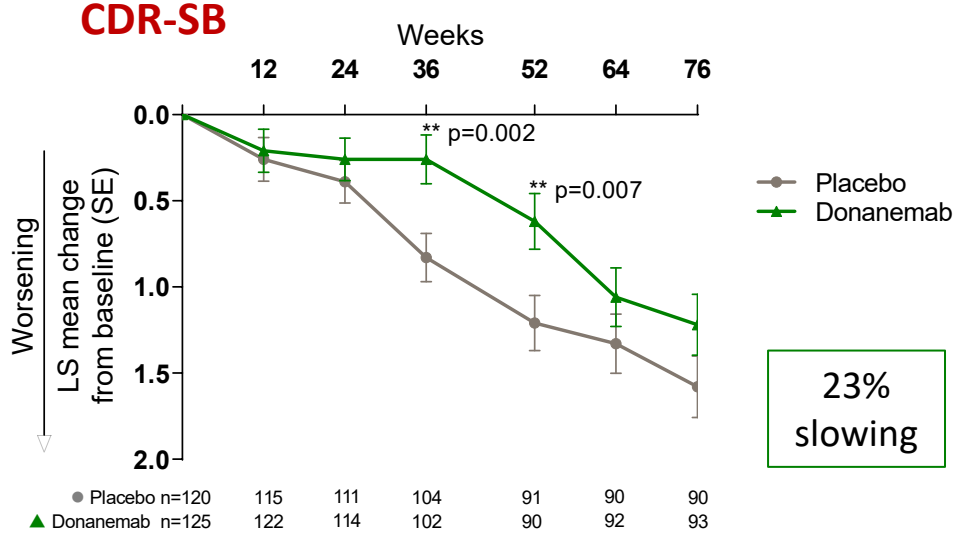
Full Analysis Set

iADRS – Primary Outcome



32% slowing

CDR-SB



23% slowing

Mintun *et al.* ADPD 2021; Mintun *et al.* NEJM 2021 DOI: 10.1056/NEJMoa2100708

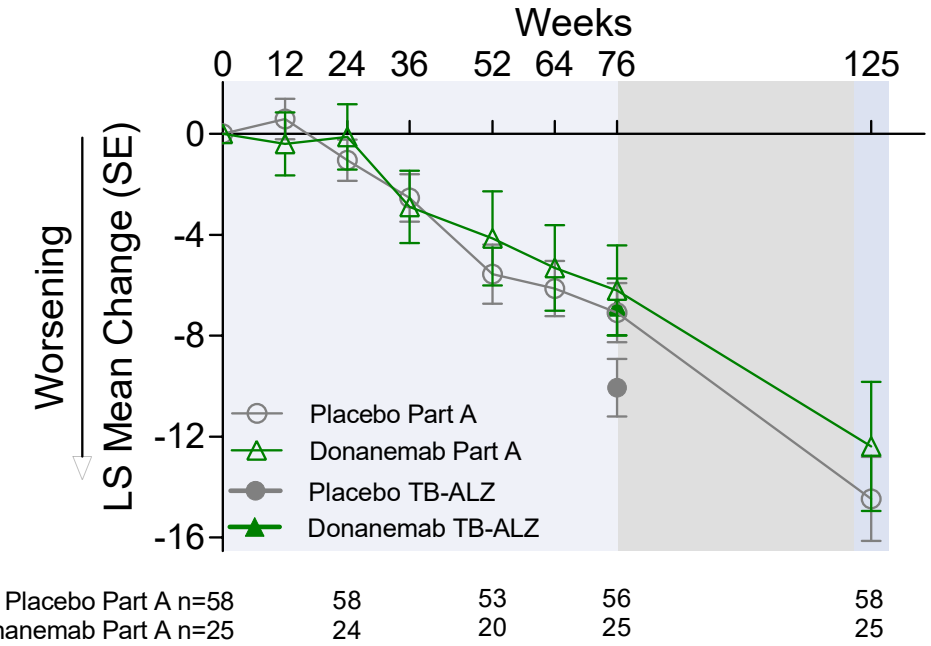
CDR-SB = Clinical Dementia Rating Scale; iADRS = Integrated Alzheimer's Disease Rating Scale; LS = Least Squares; n = number of participants; SE = Standard Error;
* p-value <0.05 versus placebo, ** p-value <0.01 versus placebo

TRAILBLAZER-EXT: Clinical Scales ~1 Year Post Donanemab Treatment for Those Participating in TB-EXT Part A

TB-EXT ppts in TB-ALZ	No Treatment	TB-EXT Part A

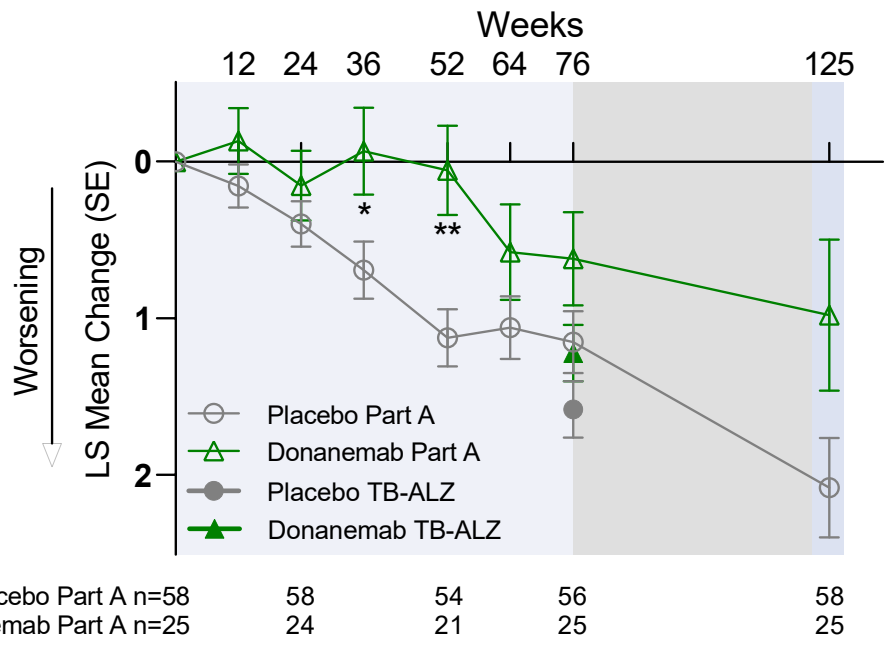
TB-EXT Population

iADRS



Placebo Part A n=58	58	53	56	58
Donanemab Part A n=25	24	20	25	25

CDR-SB



Placebo Part A n=58	58	54	56	58
Donanemab Part A n=25	24	21	25	25

Limitations include relatively small n (25, 58), returner bias (impact in placebo group), most Part A scales performed after TB-ALZ treatment assignments known

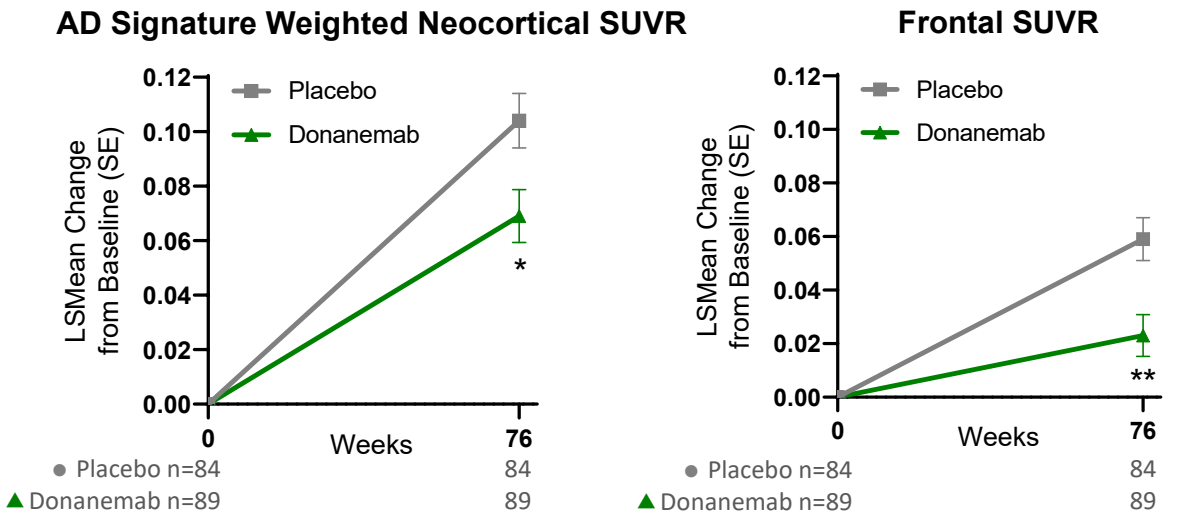
Onsite scale assessments from TB-EXT Part A; time since randomization approximate mean of 125 weeks (range 82-159 weeks). CDR-SB = Clinical Dementia Rating Scale; iADRS = Integrated Alzheimer's Disease Rating Scale; LS = Least Squares; n = # of participants; SE = Standard Error, * p-value <0.05 versus placebo, ** p-value <0.01 versus placebo

TRAILBLAZER-ALZ: Slowing of Tau Accumulation in Key Brain Regions and Reduction in Plasma P-tau217 for Donanemab vs Placebo

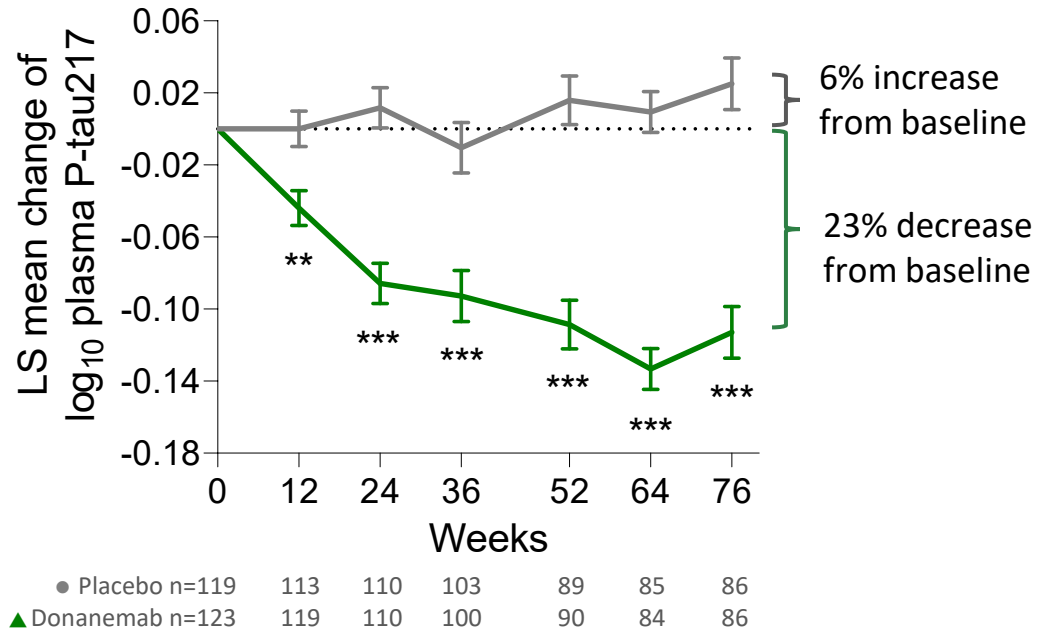
TRAILBLAZER-ALZ

Full Analysis Set

Tau PET



Plasma P-tau217



Tau PET: Shcherbinin *et al.* JAMA Neurol 2022 doi:10.1001/jamaneurol.2022.2793; Mintun *et al.* AAIC 2021; LS mean change in tau SUVR at week 76, cerebellar gray reference region
Plasma P-tau217: Adapted from Mintun *et al.* AAIC 2021; Pontecorvo *et al.* JAMA Neurol doi:10.1001/jamaneurol.2022.3392
Least square mean change from baseline in plasma P-tau217 for placebo (grey line) and donanemab (green line). Plasma values were log10 transformed. Error bars indicate standard error. Black dashed line indicates baseline. * p-value <0.05 versus placebo, ** p-value <0.01 versus placebo, *** p-value <0.001 versus placebo

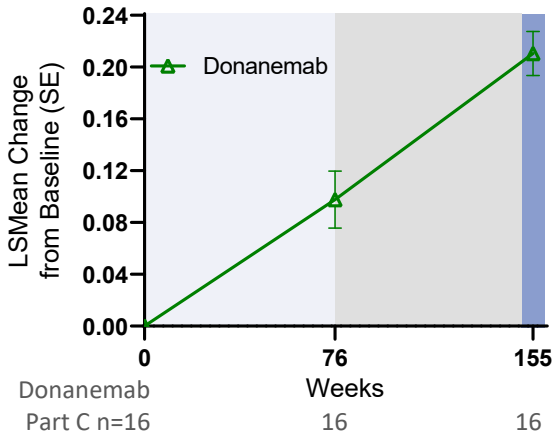
TRAILBLAZER-EXT: Tau Pathology Changes ~18 Months Post Donanemab Treatment for Those Participating in TB-EXT Part C

TB-EXT ppts in TB-ALZ	No Treatment	TB-EXT Part B	TB-EXT Part C

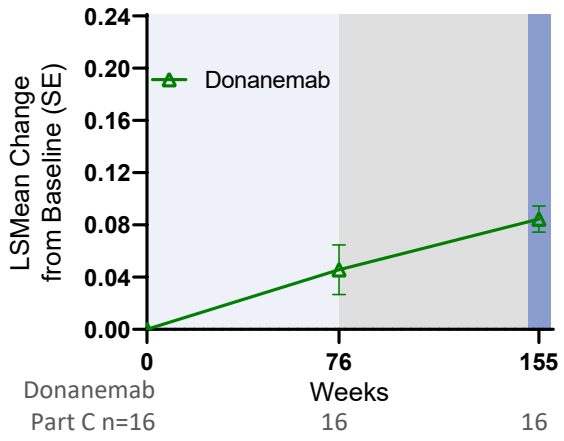
TB-EXT Population

Tau PET

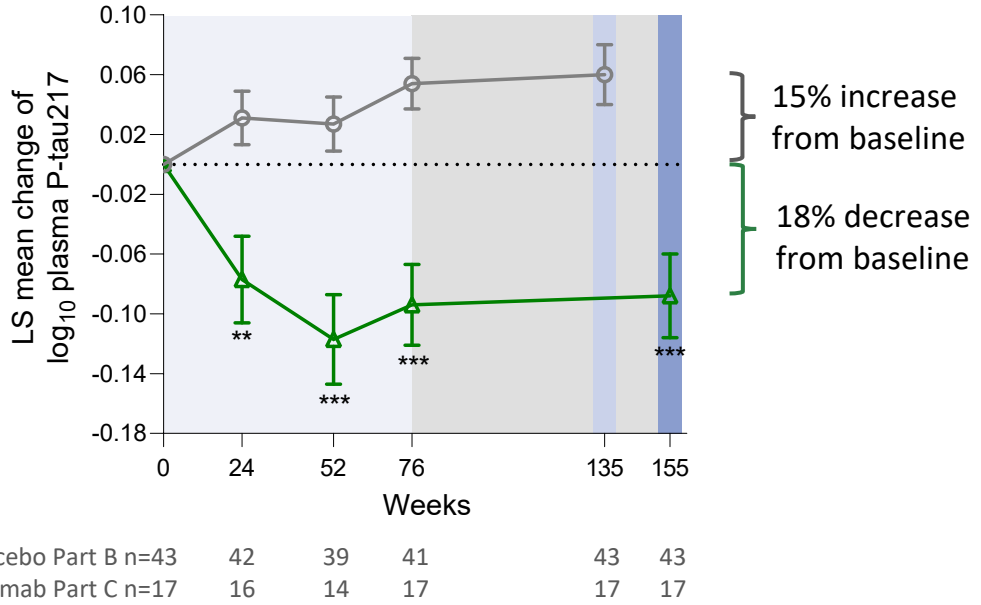
AD Signature Weighted Neocortical SUVR



Frontal SUVR



Plasma P-tau217



Tau PET: Cerebellum gray matter reference region (methods from Shcherbinin *et al.* JAMA Neurol 2022 doi:10.1001/jamaneurol.2022.2793)
Plasma P-tau217: Plasma samples from Part B Visit 1 prior to donanemab dosing were used for EXT comparator (grey line). Reran samples from TB-EXT participants with complete sets across TB-ALZ and TB-EXT; Mean time since TB-ALZ randomization placebo (grey) ~135 wks (Part B range 96-200 weeks), donanemab (green) ~155 wks (Part C range 124-211 weeks). Plasma values were log10 transformed. Error bars indicate standard error. Black dashed line indicates baseline. ** p-value <0.01 versus placebo, *** p-value <0.001 versus placebo

Summary

- Following treatment cessation, amyloid plaque reaccumulated at a rate of ~4 Centiloids per year, similar to natural history observations
- Clinical changes and aggregated tau accumulation appear to neither plateau nor accelerate after cessation of donanemab treatment
  - Tau PET and P-tau217 in the setting of amyloid-targeting treatments appear decoupled
  - Data suggest the importance of finding specific anti-aggregated tau treatments
- Plasma P-tau217 treatment difference relative to placebo generally maintained; levels remain lower than baseline ~18 months after the end of the TRAILBLAZER-ALZ trial
- Limitations include relatively small n, returner bias, most Part A scales performed after TB-ALZ treatment assignments known, and no comparator for PET data
- Phase 3 TRAILBLAZER-ALZ 2 long-term extension will provide more robust insight into long-term effects of donanemab treatment

Acknowledgements

- We gratefully acknowledge the contribution and dedication of all the trial participants with AD, their families, and their caregivers who participated in this study, along with trial site investigators and personnel, and members of the data monitoring committee
- We acknowledge contributions from Albert Lo, Mirek Brys, Alle Barnard Vanwye, Melissa Williamson, Gavin Hawkes, Genevieve McPhilemy, Arashpreet Kaur, and Staci Engle
- This study was sponsored by Eli Lilly and Company

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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 Wednesday 20 November 2024. Please submit via NICE Docs.

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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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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.
	Alzheimer's Research UK has received £24,925 in trust from Eli Lilly on behalf of the Brain Health Coalition UK, designated for building the coalition's website.
	
	Over the past 12 months, Alzheimer's Research UK has also received sponsorship from Eisai Europe Limited for the 2024 Research Conference, covering the conference platform and keynote speaker (£4,200).
	
	In addition, several projects funded under the Dementia Consortium umbrella in early 2022 are either ongoing or have been recently terminated.
	
	The Dementia Consortium brings together experts in target biology from academia and drug discovery experts from industry. The project provides funding and in-kind support for research projects typically 2 to 3 years in duration. Alzheimer's Research UK and the Dementia Consortium Industry partners, which includes Eisai, share the cost and risk of early-stage dementia drug discovery.
	
	VAPB: ER-mitochondria signalling as a new target for Dementia (VAPB-PTPIP51 tethering)
	• Status: Ongoing
	• Funding: Eisai provided £148,272.07, invoice dated 10 March 2022
	
	C9ORF72: Identification of tool compounds targeting the SRSF1-dependent nuclear export of pathological C9ORF72-repeat transcripts
	• Status: Project terminated after funding partners decision meeting in May 2023
	• Funding:
	  ○ Eisai provided £28,588.86, invoice dated 1 October 2022
	  ○ Takeda provided £23,270.10, invoice dated 31 August 2022
	
	Kings/ALS: Validating new promising drug targets in Amyotrophic Lateral Sclerosis
	• Status: Ongoing, the whole project was paid upfront by all partners
	• Funding: Takeda provided £97,377.90, invoice dated 11 November 2022

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.

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1	**Ongoing review of long-term data on donanemab is needed**. The company has extensive TRAILBLAZER study plans, with some results expected in Q4 2024 and beyond. We believe that when the company provides this data, it would be valuable for NICE to incorporate these findings into their evaluation of donanemab's long-term efficacy.
2	**We agree with the committee that further information on infusion costs is necessary**, including a detailed breakdown of expected resource use from NHS England to fully explain the estimated costs. Notably, there is a significant discrepancy between the company's cost estimate of £208 and NHS England's figure of £565. This difference suggests that if NICE's cost assumptions align with NHS England's estimate, it may have significantly impacted the ICER. We obtained estimates from three 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 suggest that the actual real-world cost of infusion may be lower than the £565 figure (approximately £300). While NHS England is the most appropriate stakeholder to provide such estimates, it would be valuable to understand the detailed rationale behind the significant difference between NHS England's figure, the company's and clinicians' estimates. It's important any analogues used to help with costing are as close to the specific technology and patient population as possible. For example, given people receiving this treatment will be in the early stages of the disease they will be relatively independent and would generally not need the sort of support people in the later stages of Alzheimer's would require in a clinical setting.
3	NICE, NHS England, and the company should **continue exploring the possibility of a managed access route** for donanemab. We support the committee's recommendation for the company to submit an updated managed access proposal that better addresses the key uncertainties and presents plausibly cost-effective ICERs. The Innovative Medicines Fund (IMF) was established to enable access to new, innovative non-oncology treatments where there was uncertainty of data on outcomes and costs. This should mean that the IMF is an appropriate vehicle for drugs like donanemab. It is important to consider the unique challenges that Alzheimer's disease presents and the innovative nature of donanemab alongside the current lack of pathway for prescribing this treatment and significant variation in diagnosis across the NHS. Allowing access to a targeted group of patients could still deliver: • meaningful insights for further research • 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.
4	We would like to understand **how the quality of life for carers was incorporated** into the evaluation process. Although this aspect is mentioned in the papers, it remains difficult to interpret, and we would appreciate receiving this information in non-technical language. Our supporters are keen to understand which aspects of carers' experiences were considered, how quality of life was measured and how this data influenced the decision-making. We know the EQ5D is generally

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	used as a measure in this area and would like to understand the criteria NICE used to assess how appropriate a measure is in truly reflecting the impact on carers. For example, the financial and productivity impacts on carers of Alzheimer's patients were not captured in the model as the committee has noted that these costs fall outside the NICE reference case. Furthermore, we are interested in how informal care costs were considered in the evaluation. While donanemab may not currently be deemed cost-effective due to other factors, nonetheless these considerations could have a substantial impact on the final ICER. A thorough assessment of the treatment's value should also consider that dementia costs are largely borne by individuals and families rather than the state. With approximately 700,000 informal carers in the UK providing 1.3 billion hours of unpaid care for dementia, translating to an estimated formal cost of £8.8 billion[i]. Given these factors, we would like to understand **if there is potential to apply the non-reference case to more accurately reflect these significant costs**.
5	We would like to understand how the MHRA's exclusion of individuals with two copies of the APOE4 gene from the label will impact the base case model, particularly since this reflects a smaller potential patient population.
6	We are 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, early treatments for Alzheimer's are 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

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.
- 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.

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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.

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.

[i] Landeiro, F, Luengo-Fernandez, R, 2021 [in preparation], 'Economic burden of cancer, CHD, dementia, and stroke 2018'
[ii] Understanding medicines access: a look at the severity modifier and its impact (abpi.org.uk)
[iii] 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.
Example 1	We are concerned that this recommendation may imply that ……..
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 the draft recommendation NICE has made whilst also recognising the disappointment that many

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	people may have experienced on learning the decision. We accept NICE's assessment that due to substantial uncertainties in the economic model it is not clear what the most likely cost-effectiveness estimate would be. We accept NICE's assessment that the cost-effectiveness is likely to be above what NICE normally considers an acceptable use of NHS resources, but include below new evidence and comments for NICE's consideration.
2	We acknowledge NICE's assessment of the lack of evidence on the long-term effects of donanemab and the substantial uncertainties in the economic model, and recognise the challenges this creates in making an assessment on cost-effectiveness. We welcome NICE asking the company and NHS England to provide additional information to help address uncertainties, and look forward to seeing further information on this.
3	We would also encourage NICE to monitor and review real-world data on the benefits and risks of donanemab being collected in countries where it is approved for use and from ongoing clinical trials. This is particularly important given MHRA's decision to approve on safety and effectiveness grounds, but with some exclusions. There are opportunities to learn more about donanemab on a real-world basis from the application of MHRA's decision.
4	It is positive that NICE have listened to the experiences of people with Alzheimer's disease, including individual patient experts and submissions from patient and carer organisations like ourselves. In particular, we welcome the recognition of the challenges the condition can bring for both the person with Alzheimer's disease and their carers, how Alzheimer's disease affects people differently, and the hope that a first potential disease-modifying treatment brings.
5	We welcome the recognition from NICE of the significant changes that would be required to the existing diagnosis and treatment pathway, which was a key point raised in our first submission. New research released since that submission has found that spending on diagnosis and treatment for dementia is equivalent to just 1.4% of dementia healthcare costs, whilst by contrast, unplanned hospital admissions make up almost a third of all dementia healthcare costs[1]. This demonstrates the lack of prioritisation of proactive and preventative care for dementia. Changes to the diagnostic pathway are urgently needed to increase access to the symptomatic treatments and interventions recommended by NICE. Further changes will be required to rollout the diagnostics needed to confirm eligibility for disease modifying treatments that may be approved in the future.
6	We welcome the recognition from NICE that inequalities may increase as existing services already under strain would be needed to deliver treatment. We also note a further important point from NICE about equality, that people with Down's syndrome, people with young-onset dementia and people from ethnic minority backgrounds were not fully represented in the TRAILBLAZER-ALZ 2 clinical trial, and that these people are at risk of being excluded from accessing donanemab. We urge NICE to continue to consider the impact of donanemab on inequalities.
7	Alzheimer's Society has new evidence which has been published since the Society's submission to the NICE appraisal for donanemab in February 2024. This is evidence commissioned from healthcare consultancy Carnall Farrar, on the scale, cost and impact of dementia, and evidence relevant to this appraisal will be presented in this submission.
8	Prevalence of Alzheimer's disease can be relevant to calculations of cost effectiveness of donanemab due to increasing economies of scale. It is estimated that there are around one million people with dementia in the UK; and this is set to rise to 1.4 million by 2040[2]. It is estimated that

[1] https://www.alzheimers.org.uk/about-us/policy-and-influencing/dementia-scale-impact-numbers
[2] Ibid

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	50% of people with dementia have mild dementia, 37% moderate dementia, and 13% severe dementia[3]. Estimates of the prevalence of Alzheimer's disease, from previous research, are that this accounts for between 50% and 75% of all cases of dementia[4] (sometimes co-existing with vascular dementia). This is consistent with the estimate used by NICE, that 6 in 10 people with dementia have Alzheimer's disease. The new evidence from Carnall Farrar did not produce estimates of the possible population eligible for DMTs for Alzheimer's disease but the estimates of future prevalence and disease severity may help with these calculations.
9	The current cost of dementia could be useful context to the appraisal of donanemab. The total cost of dementia in the UK each year is £42billion; and this is set to rise to £90billion by 2040[5]. Unpaid care accounts for 50% of the total cost (£21.1bn), social care accounts for 40% (17.2bn), and healthcare accounts for 17% (£7.1bn)[6].
10	The draft guidance recognises that currently a third of people with dementia do not have a diagnosis. It also states that 'NHS England advised that introducing disease-modifying treatments would substantially increase demand on primary care and memory clinics because of increased awareness of MCI and availability of treatment options'. Our first submission set out evidence for the benefits of diagnosis for individuals, including unlocking access to support, care and symptomatic treatments. Although creating capacity challenges for memory services in the short to medium term, more people with dementia getting a diagnosis would be a positive development. We would also like to share that new evidence has found that a cohort of people with undiagnosed dementia attend A&E, on average, 1.5 times per year; which is three times as much as people with similar characteristics without dementia (in a control group matched for age and comorbidity), and more than people with diagnosed dementia of any level of severity[7]. This suggests a further value to diagnosis, in reducing the need for emergency care.
11	As the condition progresses, people with dementia spend longer in hospital for non-elective stays: on average, each year a person with severe dementia stays in hospital three times as long as someone with mild dementia (27.7 days vs 9.3 days)[8]. This could indicate potential benefits of reducing demand on hospital resources from donanemab where it can delay progression through the stages of Alzheimer's disease.
12	As the condition progresses, the average cost of dementia per person rises significantly: from £29,000 per year for mild dementia, to £43,000 per year for moderate dementia, to £81,000 per year for severe dementia[9]. A key driver of the high costs for severe dementia is the need for social care. This could indicate potential cost savings from donanemab where it can delay progression through the stages of Alzheimer's disease. There could also be benefits in reducing demand for social care. It is projected that by 2040, 76,000 more people with dementia will live in a residential home and 30,000 more in a nursing home[10]. It is also projected that by 2040, 61,000 more people with dementia are projected to be drawing on domiciliary care[11].

[3] Ibid
[4] https://www.alzheimers.org.uk/sites/default/files/migrate/downloads/dementia_uk_update.pdf
[5] https://www.alzheimers.org.uk/about-us/policy-and-influencing/dementia-scale-impact-numbers
[6] Ibid
[7] https://www.alzheimers.org.uk/about-us/policy-and-influencing/dementia-metrics-early-diagnosis-and-treatment
[8] https://www.alzheimers.org.uk/about-us/policy-and-influencing/dementia-metrics-early-diagnosis-and-treatment
[9] Ibid
[10] Ibid
[11] Ibid

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

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13	Carnall Farrar developed estimates of the potential cost savings of early diagnosis and treatment with acetylcholinesterase (AChE) inhibitors such as donepezil. Though these treatments aren't suitable for everyone with Alzheimer's disease, where they are effective, some research has found they have the potential to delay admission to residential care; though evidence is mixed, and more research is needed. Modelling suggests that the delay to admission to residential care could result in savings of up to £9,000 to £45,000 per eligible person[12]. These savings are distributed across the individual and their family and the state. It is possible that savings related to social care could be achieved by donanemab if it is shown to delay admission to residential care.
15	NICE report that the impact on the finances and productivity of carers for people with Alzheimer's disease were not captured in their model. We would like to share some evidence on the impact of dementia on the finances and productivity of carers, for NICE's consideration. Over 147,000 working age carers supporting a person with dementia, have had to reduce their work commitments, or are having difficulty balancing work and caring[13]. A total of 112,540 are no longer in paid employment due to their caring responsibilities[14]. 39% of carers for people living with dementia are providing over 100 hours of care a week, and 60% are providing over 35 hours of care per week[15].
16	On mild cognitive impairment (MCI), the draft guidance notes that some people are followed up after an MCI diagnosis, but many are discharged back to primary care with the advice to be re-referred once symptoms progress. The draft guidance also notes that there are challenges with diagnosis of MCI in NHS clinical practice. Alzheimer's Society believe there is a need for greater guidance on MCI and has called for this to be included in the NG97 guideline.

Insert extra rows as needed

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[12] https://www.alzheimers.org.uk/about-us/policy-and-influencing/dementia-metrics-early-diagnosis-and-treatment
[13] https://www.alzheimers.org.uk/sites/default/files/2019-10/The%20economic%20cost%20of%20dementia%20to%20English%20businesses%20-%202019%20refresh%20-%20Final%20complete.pdf
[14] Ibid
[15] https://digital.nhs.uk/data-and-information/publications/statistical/personal-social-services-survey-of-adult-carers/england-2021-22

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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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Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	Nil
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	Molecular diagnostics for Alzheimer's disease are already contained within NICE guidance (NG97) and should ideally be routinely available to support clinical diagnosis (although they are currently only available in about 5% of services). It is arguable whether the costs associated with molecular confirmation of Alzheimer's disease pathology (CSF and/or amyloid PET) should be factored into cost effectiveness.

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2	We would like to understand more about why the severity modifier was not applicable to Alzheimer's disease despite it being the leading cause of death in England.
3	The costs associated with Alzheimer's disease include both the economic costs of unpaid family carers and the reduction in quality of life associated with being a carer. We would question why it is not appropriate to factor these into health economic modelling.
4	There is no current NICE guidance on diagnosis and management of mild cognitive impairment. Whilst we recognise that this is outside the remit of the TA committee, we feel that future evaluations would benefit from clearer standards of (molecular) diagnosis and care for MCI.
5	There are major differences in the estimated costs of iv infusions between the company and NHS England. We would ask what factors have been considered in deciding which estimate best reflects real world costs (including the need for new infrastructure – e.g. infusion space - but also potential economies of scale). We are also uncertain whether the proposed tariff is just for infusion, or also serves to collect data around safety monitoring.
6	We are uncertain as to whether the suggested re-costings by ApoE4 status also model a scenario excluding E4 homozygotes. As the MHRA licence preclude these individuals from receiving treatment with Donanemab we feel this is most realistic scenario to model.
7	We consider the likelihood of individuals stopping Donanemab prior to 18m due to having evidence of amyloid clearance as demonstrated by PET to be far smaller than 10%. We would suggest a much more likely and practical scenario would be for all eligible patients to receive 18m of infusions, and so not model a scenario where some individuals have follow-up PET scans.
8	We note the committee's request for more evidence and invitation of an updated managed access proposal. We consider that an appropriately designed managed access scheme may have the potential to resolve uncertainties around real-world benefits and longer-term transitions between disease states. We consider that the NHS would be the ideal setting for such a study, and the only way to resolve some of the specific considerations around real-world use in the UK. We would be keen that longer term data are not acquired only in less representative settings such as private care and international health systems not directly applicable to the NHS.

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):	College of Mental Health Pharmacy (CMHP)

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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.
Example 1	We are concerned that this recommendation may imply that ……..
1.	We agree that all the relevant evidence that is presently available has been considered.

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2.	Summaries of clinical and cost effectiveness are reasonable interpretations of the evidence With regards to the primary outcome measure our members highlighted: A meaningful change in the integrated Alzheimer's Disease rating scale, measuring both cognition and functioning is considered to be, five points for people with Alzheimer's who have mild cognitive impairment and nine points for people with Alzheimer's who have mild dementia. Change in the scale from the start of the trial to 76 weeks was −10.19 in patients receiving donanemab compared with −13.11 in patients receiving a placebo. This difference of 2.92, is less than what is considered to be a meaningful change for patients.
3.	The recommendations are sound and of a suitable basis for NHS guidance. However, our members pointed out the following considerations: - Identification of patients in the early stages of Alzheimer's would require the development of specialist diagnostic clinics to test and confirm potential underlying disease. Does the severity of AD need to be considered better by the NICE model. - Current memory and dementia services throughout the UK are not well geared currently to deliver Monoclonal Anti-Body (MAB) infusion therapy with the required monitoring and equipment to manage infusion related adverse reactions. A substantial number of services will not be linked or in proximity geographically to acute medical services. Access and availability to PET scans throughout the UK for diagnosis and ongoing monitoring is also another consideration. - Side-effect burden is substantial, and like all novel medicines more side-effects will become apparent when used in day-to-day practice. Management of brain swelling and bleeding as well as hypersensitivity reactions need to be considered. How these will be monitored, managed and the impact on services need to treat such, needs to be considered especially with respect to the above point regarding proximity of acute medical services. For the above reasons our members agree that the costs on the system needing to be developed around this new medication are onerous and not clearly defined.
4	Our members did not think that any aspect of the recommendations needed particular consideration to ensure unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation. However**,** Alzheimer's Disease risk is increased by poverty (access to hearing aids, smoking, diabetes, depression etc) limiting treatments on the NHS may arguably influence marginalised communities. Clearly age is a non-modifiable risk component and women are more likely to develop AD due to their longevity.
5	Genetic results given to such patients, may also then prompt requests in APOE4 allele testing for closely related family members. Hence genetic counselling to the patient and its impact on close relatives need to be considered. This is especially pertinent considering the increasing availability of private genomic testing and how primary care physicians will have to deal and manage the concerns from family members ascertaining their APOE4 status via private routes.
6	We agree that more evidence is needed especially with regards to: - Longer term outcomes of treatment and stopping. - The impact of adverse events, their management and the types of services required to treat these - The cost effectiveness of the treatment considering the wider impact to the system
7	The clear need for this group of patents is social care and support. Government after government has identified the need to invest in and reform social care. This, along with more focused efforts in dementia prevention need to be the priority, rather than spending money on drugs of questionable benefit.

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):	Faculty of Public Health

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1	• **Has all of the relevant evidence been taken into account?** As noted in the comments below, the exclusion criteria applied in the trials, and the high screening failure rate in the trials, are clearly relevant to considerations about generalising the trial cohorts to the general population; as is the 10-year average age

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	difference between the trial cohorts and the development of dementia in the population. These are absent/inadequately considered in the draft guidance.
2	• **Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?** Consideration of attrition bias, particularly in censored analyses, could be added. Consideration of the costs of eligibility screening is needed. 79% of those screened for eligibility in the phase III trial were excluded (i.e. for everyone 5 people who underwent checks including PET/CSF, MRI, genotyping... 4 were excluded). At the moment the costs are only considered for the 1/5 included, not the 4/5 excluded. If the same eligibility criteria would not be applied in clinical practice, then the committee's assertion that "the trial cohorts are generalisable to the UK clinic population" clearly does not hold and the implications of this should be introduced into the modelling (i.e. a likely blunting of treatment effect and increase in adverse event likelihood).
3	• **Section 3.1: Alzheimer's disease** "More than 95% of people affected are over 65 years." Regarding considerations of the generalisability of the trial cohorts to the general population with dementia, it would be additionally meaningful here to note that the average age of dementia onset was around 83 in the population-based MRC CFAS II studies, 10 years older on average than the trial cohort. Simply listing that most people are >65 does not highlight this significant gap.
4	• **Section 3.2: Diagnosing mild cognitive impairment and mild dementia caused by Alzheimer's disease** "can be confirmed" please add "can be confirmed *in someone with symptoms* by the presence of…" The majority of those with asymptomatic amyloidosis do not develop dementia in their lifetime (Brookmeyer 2019 Alzheimer's & Dementia, Jack 2022 Brain)
5	• **Section 3.2: Diagnosing mild cognitive impairment and mild dementia caused by Alzheimer's disease** "The clinical experts emphasised that all people with mild cognitive impairment caused by Alzheimer's disease eventually progress to having dementia."

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	This line has been used in both the lecanemab and donanemab guidance. It is clearly a very important consideration. It was not discussed properly in the 2nd (open) committee meeting of lecanemab. This assertion that all patients with 'MCI caused by AD' will progress is not supported by a reference. We are not aware of any epidemiological evidence that supports it. It is accepted that some cases of MCI resolve. Whether that is different for people with MCI attributed to AD is likely to be contingent on the definition of 'MCI caused by AD' used, the timeframe of follow up, and any selection biases in the clinical cohort used to examine this question (assuming it is not based on population-based studies). The guidance should be clear whether this statement is supported by evidence. If this is the case, it would be helpful to report the definition, cohort used, and follow-up time. Or if not, it should be labelled as 'clinical opinion without supporting empirical evidence'.
6	• **Section 3.2: Diagnosing mild cognitive impairment and mild dementia caused by Alzheimer's disease** The clinical experts advised that “there are no standardised measures to clearly separate the disease stages.” This being the case, it is difficult to see how the same clinical experts can be sure that all patients will progress from one stage to the other (see previous comment).
7	• **Section 3.5: Clinical trials** “This included having low-to-medium or high levels of tau protein on a PET scan. TRAILBLAZER-ALZ 2 was done in 277 sites in 8 countries including the UK. The trial randomised 1,736 people; 860 had donanemab and 876 had placebo. Overall, 76% of patients completed the 76-week study. The mean age was 73 years and 57% were women.” This description of the study should also include a summary of the exclusion criteria which were extensive and led to some of the concerns about lack of generalisability. For reference, they included: Any condition (other than AD) that might be causing cognitive impairment. Alcohol or substance abuse, last 2 years. Any psychiatric disorder which may affect study analysis, any history of psychosis. Cancer in last 5 years. Hepatic impairment. Low literacy, visual impairment, or hearing impairment affecting neuropsychological testing. Multiple or severe drug allergies. Any serious or unstable medical condition, or clinical abnormalities in physical examination, vital signs, lab tests, or ECG, that the PI considers may affect study analyses. >4 Micro- or any macro-haemorrhages, >1 area of superficial siderosis, severe white matter disease, or any MRI evidence that could indicate a non-AD dementia
8	• **Section 3.5: Clinical trials**

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	"The committee decided that results from TRAILBLAZER-ALZ 2 and TRAILBLAZER-ALZ would be generalisable to people who might have donanemab in NHS clinical practice." Please could the committee explain on what epidemiological basis they rejected the FPH expert opinion that this is not the case, and instead made this judgement that generalisability could be assumed? This judgement is not currently explained, merely stated. The trial cohort were 10 years younger, on average, than people developing dementia in the population (MRC CFAS II data). Those with co-morbidities and co-pathologies, which is very frequently seen in those with dementia in the population, were mostly excluded. The trial cohorts are clearly not generalisable to all people living with a diagnosis of Alzheimer's disease in the population, but specifically to those who present early and without mixed pathologies driving their cognitive impairment (which is what is usually seen for the late-life dementia syndrome).
9	• **Section 3.7: Clinical-effectiveness results** "Faculty of Public Health stated it was unclear if the trial results were clinically meaningful" In fact, our submission did not suggest this was unclear. We presented the existing empirical evidence on this question. This evidence is clear that this effect is not clinically meaningful.
10	• **Section 3.8: Risks of bias** This is a very important consideration when appraising the trial evidence. NICE may reflect on why this same section was not present in the lecanemab draft guidance. These same risks of bias were present in that trial as well (and we highlighted them in our evidence submission).
11	• **Section 3.8: Risks of bias** "The company produced hazard ratios for disease progression with censoring for ARIA and infusion-related reactions." Censoring those from the treatment group that experience adverse events will correct for unblinding, but it will exacerbate the attrition bias (in which only those who are doing well on the treatment are included in the analyses at later time points). It would therefore be appropriate to additionally report the treatment effects stratified by adverse events (e.g. ARIA).
12	• **Section 3.8: Risks of bias** "The company's results are confidential and cannot be reported here."

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

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	It is not clear why the results of this sensitivity analysis, in which missing data were imputed, should be confidential? These data are important for public appraisal of the evidence.
13	• **Section 3.10: Subgroup effects by standard care treatment** "It also noted that people entering the trials had higher than expected use of acetylcholinesterase inhibitors or memantine (about 60%). One of the EAG's clinical experts estimated that in UK clinical practice, a minority (below 20%) of people with mild cognitive impairment caused by Alzheimer's disease have acetylcholinesterase inhibitors and none have memantine." This further challenges the committee's opinion that the trial cohort is generalisable to standard NHS patients with 'early AD'.
14	• **Section 3.13: Long-term assumptions for full treatment effect** "The clinical experts advised there is great uncertainty about the potential long-term treatment effects of donanemab." It is perhaps worth noting here that a further source of uncertainty about long-term effects comes from the adverse effects - haemorrhages and brain shrinkage are predictive of future cognitive decline in population-based studies. Though trial evidence was reassuring that these were typically asymptomatic and self-limiting, the longer-term effects are unclear.
15	• **Section 3.16: Costs** It appears that the costs of eligibility testing were not included in the modelling from the company or the EAG? In the trial, 79% of those referred for eligibility testing by specialists were found to be ineligible, either due to low amyloid levels, or because of the exclusion criteria. This therefore represents a significant cost, performing either PET scans or lumbar punctures, and MRI scans, and genotyping on (up to 4 times) more people that go on to actually receive the drug. These are real, quantifiable, costs and resources that will affect the whole dementia care pathway and produce significant opportunity costs to the system and its patients. It is unclear why they would not be included in this modelling. An alternative is that the criteria for treatment would be less stringent in practice than they were in the trials. If that is the case, then the modelling must try and account for this lack of generalisability, and the likely effects of this broadening of eligibility (blunting of treatment effect and increased rate of adverse events).
16	• **Section 3.18: Outpatient consultation visits** "EAG added 1 outpatient consultant visit at diagnosis"

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	Is this for only those that have already been eligibility screened? (i.e. the patient has a clinical diagnosis, then a PET or CSF sample to confirm inclusion criteria, then an MRI to confirm an absence of exclusion criteria, and then the genotyping). Or does this all occur at the same time - in which case it will need to be modelled for a much larger group of people than those ultimately eligible, given the high screening failure rate (79%) in the trial.

Insert extra rows as needed

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- Combine all comments from your organisation into one response. We cannot accept more than one set of comments from each organisation.
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- 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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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Royal College of Psychiatrists

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Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	[Insert disclosure here]
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	On behalf of the Old Age Psychiatry Faculty, RCPsych thank you for the opportunity to comment on the draft guidance for donanemab. Our main comment is to know whether managed access represents a feasible option?

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	Managed access could help address current uncertainties in evidence regarding real world efficacy and safety including subgroup analyses; help establish diagnostic and treatment infrastructure that currently needs developing; and over the next 2 years we anticipate blood-based biomarkers (that are already commercially available) will be approved for clinical use and this is anticipated to significantly reduce diagnostic costs associated with using this treatment (as well as improving patient experience). We would also anticipate further cost lowering (eg relating to the administration of the treatment – notably infusion costs) should a subcutaneous formulation become available in the future (naturally depending on marketing and MHRA developments).
2	
3	
4	
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):	UK Clinical Pharmacy Association (UKCPA)

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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.
Example 1	We are concerned that this recommendation may imply that ……..
1	We have some concerns around service capacity, in particular, outpatient visits (which should be included in the cost), lumbar puncture, genetic testing. We are also concerned that a delay in

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	diagnosis can limit access due to progression of the disease, by shifting the eligibility. We are conscious of different service capacities in different areas, which can have an impact on which patients can have access to the treatment.
2	In relation to equality and diversity, patients with Down syndrome, young onset dementia and some ethnic groups were not adequately represented in the trails, this pose a risk of potential adverse impact that has not been established yet, should the company explore more the impact of donanemab in these populations?
3	From our perspective, there is a need of investment and remodelling of the service for this patient group but also for more advance disease, and this should be considered when evaluating that the benefit for the population will outweigh the safety concerns and investment required.
4	Since PET is not mandatory to start donanemab and the limited availability of PET scans in the country, it's unlikely that patients will stop treatment before 18 months due to clearance. We also agree that mortality is higher in severe AD and this should be taken into account from the company to predict mortality.
5	
6	

Insert extra rows as needed

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Donanemab Consultation Response to NICE on Infusion Costs and Treatment Duration

Infusion Costing

Summary

In response to the publication of the draft NICE appraisal recommendations for both lecanemab and donanemab, NHS England has undertaken a further review of infusion pricing options. Should a positive adoption recommendation be made by NICE, these costs would be met by integrated care boards (ICBs) as the responsible commissioners for most elements of the Alzheimer's clinical pathway. We believe that an appropriate alternative method for estimating the costs for modelling and appraisal purposes is to use an approach consistent with the pricing assumed within the NICE appraisal process for monoclonal antibodies (MABs) administered in the management of a confirmed COVID infection. Using this method, and subject to a coding guidance and practice change, NHS England's pricing team estimate a resulting indicative unit price, including Market Forces Factor (MFF), of £432.

Background

NHS England notes that within the appraisal process for donanemab, a significantly lower price for the administration of an intravenous infusion has been proposed by the manufacturer, compared to the cost estimated by the NHS. NICE has subsequently requested further information from NHS England to inform further committee deliberation on this element of the wider cost-effectiveness assessment.

The costs of infusion are an important and potentially material element of the donanemab cost effectiveness calculation, but NHS England would encourage some caution in focusing on only one element of costing, since NHS pricing typically works by charging healthcare activity to the relevant NHS commissioner based on established average resource requirements. NHS pricing is not based on costing episodes of care for an individual patient nor producing granular pricing specific to every combination of procedure, patient age, complexity or medical condition.

All costings within NHS England's submission are consistent with this 'average cost' principle, in most cases using published tariff (pricing) information to cost each step in the pathway. We have not for example suggested that outpatient, MRI or lumbar puncture costs should be varied from standard tariff, even though it is possible that actual resource requirements might differ from (and even be higher than) average for the specific cohort of patients potentially eligible for AD disease modifying treatments.

NHS England's response, effectively on behalf of ICBs - the responsible commissioners (funders) of donanemab infusions if routinely introduced into NHS care - is set out below:

Basis of NHS England's original infusion costing submission for donanemab

As a recap, NHS England's original costing estimate submitted to NICE for the administration of donanemab by infusion was based – as per the approach throughout our modelling - on identifying the average cost / tariff most likely to be charged under current NHS coding and pricing guidance. This charge would be made by NHS infusion clinics to ICBs as the responsible commissioners of this element of the pathway.

- There is not currently a specific NHS price for the infusion of donanemab in the treatment of Alzheimer's disease
- Instead, based on current coding guidance, NHS England believes that the most likely price to be charged to ICBs based on recording an infusion procedure, administered as a day-case (non-admitted) attendance, and where a patient has a recorded diagnosis of Alzheimer's disease is £585. In this scenario, under the 'grouping' process that is undertaken to derive price, it is the patient's diagnosis and day attendance which are the primary drivers of the predicted average resource requirements, rather than the procedure itself.
- NHS prices are derived based on a combination of the procedure undertaken and other factors, such as the medical condition for which the procedure is being undertaken, age, length of stay etc. NHS England's infusion administration cost estimates are based on an assumption that the appropriate OPCS code for the delivery of donanemab is X292: *Continuous intravenous infusion of therapeutic substance NEC*. The Health Resource Group (HRG) grouper does not consider X292 to be resource significant, so it ignores it when grouping to an HRG. If there are no other OPCS procedure codes present for the patient's care episode, then the grouper will use the diagnosis - ICD10 - code to determine the HRG instead.
- NHS England has checked the latest HRG Code to Group file, and listed the relevant ICD10 codes which group to WD02Z in Appendix 1. NHSE believes the patient spell would be coded to one of these together with X292 for the procedure. WD02Z is listed on tab 14a of Annex A of the recently published 2024-25 update. The status of WD02Z remains unchanged i.e. it does not have a national published price and the currency is not mandated. However, this is how we would think most providers would code the activity if submitting the patient care episode to SUS.
- The average cost of an infusion (X292) for other conditions is £585.43. The cost for WD02Z from the latest available National Cost Collection (2021/22) is £660.10.
- ICD10 codes mapping to WD02Z are set out in Appendix 1.

Use of a chemotherapy tariff as a proxy for the cost of donanemab infusion

NHS England does not agree that a lower chemotherapy tariff, as proposed by the manufacturer, is an appropriate proxy for the likely costs of administering donanemab by infusion. Donanemab requires more complex preparation prior to its administration and carries a higher risk of adverse infusion reactions which will impact on treatment administration, monitoring and staffing requirements. The cohort of patients potentially eligible for donanemab will be older, and may also have more complex needs, on average, than those receiving chemotherapy.

If the manufacturer believes that additional assessment might be undertaken alongside treatment administration, such as follow up assessments of Alzheimer's disease stage (noting progression to moderate AD as a potential stopping criterion) then this would also add to resource / staffing requirements.

Please provide further detail about the source and derivation of the cost code

The information used to calculate the infusion cost for disease modifying treatment comes from the NHS Secondary Uses Service (SUS) system. SUS is the single, comprehensive repository for healthcare data in England. SUS enables a range of reporting and analyses to support the NHS in the delivery of healthcare services.

Secondary Uses Service (SUS) - NHS England Digital

Tariff prices have traditionally been based on the average cost of services reported by NHS providers in the mandatory reference costs collection, which is conducted annually. These 'reference costs' from which the tariff is produced for any given financial year are three years in arrears. Therefore, in any given year, an uplift is applied which reflects pay and price pressures in the NHS and includes an efficiency requirement.

Please give estimates of the resource use anticipated to be associated with the cost code e.g. x hours of nurse time etc

It is not currently possible to undertake a bespoke bottom-up costing exercise for ldonanemab infusion as this treatment is not currently routinely available to cost in actual clinical practice in the NHS. Even though there may be some limited donanemab use under trial conditions (largely led by academic units), this is unlikely to be in an equivalent setting nor represent the actual costs relevant to routine clinical care, nor is activity being undertaken in sufficient numbers to provide a robust basis for costing. The creation of a new price specific to the infusion of donanemab would also have implications for other NHS pricing structures and could not therefore be progressed in isolation. This might be

considered in the future should a positive recommendation be made for routine adoption of this treatment in the NHS and if uptake is material.

Proposed Alternative Pricing Approach (Parity with COVID MAB Infusion Pricing)

NHS England is content to offer an alternative pricing approach which would essentially piggyback, and be consistent with, the pricing assumed within the NICE appraisal process for monoclonal antibodies (MABs) administered in the management of a confirmed COVID infection. In this scenario it is the recording of the administration of a high-cost monoclonal antibody which would drive the price paid.

The benefit of this approach is that:

- Pricing in this area is already supported by bottom-up costing work previously undertaken by COVID Medicines Delivery Units (CMDUs) and is based on actual clinical practice, as well as consideration of prices being paid currently by commissioners for MAB infusions (where the specific MAB is overtly coded)
- Costs reflect the specific resource implications (medicine preparation, treatment monitoring requirements etc.) of the infusion of a monoclonal antibody rather than using another type of drug as an arbitrary proxy
- An equivalent minor change to NHS coding guidance could be enacted for the 25/26 financial year. Infusion clinic providers would need to ensure that the administration of donanemab is specifically captured within SUS to trigger this pricing option.

The infusion 'spells' are expected to group to the core HRG *WD02Z Alzheimer's Disease or Dementia, treated by a Non-Specialist Mental Health Service Provider*. This is diagnosis driven HRG. If there is another significant procedure recorded or undertaken during the episode of care, then it will likely mapped to elsewhere in the HRG classification structure.

Prices calculated using 2022/23 cost data and 2022/23 HES activities will generate a core HRG for WD02Z. Any drugs administered in relation OPCS 4 code(s) of *X891 or X892: Monoclonal antibodies Band 1 or 2* will generate unbundled HRGs for high-cost drugs (XD19Z or XD20Z).

Infusion of nMABs in the treatment of Mild Cognitive Impairment (MCI) or mild dementia caused by Alzheimer's Disease (AD) is a new service. Activity would be expected to be recorded as a planned day case by acute (hospital) providers who submit activity to SUS. However the price would also be applicable if activity was recorded as an outpatient procedure. The price would also be used by ICBs to agree contract values with community providers if / where activity does not flow through SUS.

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 – which is 3.6% for 22/23, 4.1% for 23/24 and 3.9% for 24/25 (this was 0.6% but has recently been increased to reflect the national pay negotiations), plus average MFF.

Please explain how this cost compares with delivery of other IV medicines – e.g. monoclonal antibodies in other neurological conditions, for COVID-19 and chemotherapy and if there are differences, the reasons for these

As set out above, the proposed revised approach, which reduces the NHS's cost estimate of administering donanemab by infusion from £585 to £432, would be consistent with the costings proposed for the infusion of monoclonal antibodies in the treatment of COVID. This was supported by bottom-up costing work undertaken on the basis of actual NHS use of monoclonal antibodies administered by infusion, by a sub-set of COVID Medicine Delivery Units (CMDUs), as well as costs paid for other infusions where monoclonal antibody use has been specifically coded by the provider / hospital.

Please note this approach would require a minor update to the annual coding guidance provided to NHS providers, and providers to specifically record the administration of donanemab in SUS.

In the scenario where DMTs for Alzheimer's are recommended for use in the NHS (through routine commissioning or managed access), please comment on whether NHSE would conduct an exercise to review this cost code after a period of data collection and how long such an exercise would take'

NHS England routinely reviews the calculations underpinning NHS pricing, and we would want to ensure this consistent process would also be used in this case. This standard review process uses data three years in arrears, using actual 'reference' costs submitted by multiple providers. The price used for infusion spell will therefore be automatically reviewed in due course using the standard reference cost process once sufficient patient volumes are available to make a calculation on average costs reliable.

Treatment Duration

We note that NICE has also requested further information from the company and NHS England that fully explains the estimated proportion of people who stop donanemab before 18 months based on amyloid-PET scan results (as per section 3.13). Please see NHS England's response to this query, below.

Within NHS England's modelling of the diagnostic, treatment and safety monitoring required for donanemab, we have noted two potential treatment scenarios, which each have different impacts on expected activity and costs. The assumptions are based on information provided to NHS England by Eli Lilly and / or information available within the product's licence. NHS England does not hold any independent information on which to base its modelling of donanemab treatment duration.

Scenario 1 (PET-CT Scanning for Amyloid Clearance at 6 and 12 months). Please note that this scenario is dependent on NHS England securing sufficient radiotracer supply and PET-CT scanning capacity, which will also be required for some patients in the diagnostic phase of the clinical pathway, prior to treatment initiation. In treatment duration scenario 1, NHS England has assumed (based on company provided intelligence) that 15% of treated patients scanned at 6 months will have demonstrated amyloid clearance and will therefore be able to cease treatment, and that a further 17% (32% in total) will have demonstrated amyloid clearance by the 12 month scan, and will therefore cease treatment at that point, rather than continue to a potential maximum 18 months treatment duration. This scenario results in an average treatment duration of 1.2 years, or approximately 62 weeks (again confirmed with Eli Lilly). Please note that we have also now assumed that the diagnostic test for amyloid clearance would need to be PET-CT only, rather than a mixture of PET and lumbar puncture / CSF, as we had originally modelled. We have changed this assumption to PET-CT only based on dialogue with the company.

Scenario 2 (Treatment Instead Continues for 18 Months). In this scenario we have modelled activity and costs based on a treatment duration of 1.5 years (18 months). If PET scanning capacity is not available, it is likely that a 'maximum 18 months' treatment protocol would be adopted in clinical practice. This scenario would overestimate average treatment duration as some patients would in practice cease treatment for reasons other than demonstrated amyloid clearance, including patient choice and progression to moderate Alzheimer's disease.

NHS England's latest modelling assumes that 1 in 7 patients initially presenting within primary care with potential symptoms of MCI or mild AD ultimately progress to treatment with donanemab. This is a change to the previous estimated ratio of 1 in 6, reflecting the impact of the MHRA's licensing decision to exclude APOE-4 homozygotes, which reduces the percentage of patients potentially eligible for, and therefore progressing to, treatment. We have also amended our modelling to include a revised infusion price of £432, based on our consultation submission.

In a steady state adoption scenario, the treatment duration scenario 1, above, produces an average cost per patient treated (incorporating the infusion pricing change already notified, and the impact of the licensing decision to exclude APOE-4 homozygotes) of [redacted], and treatment duration scenario 2 produces an average cost per patient treated of [redacted]. We believe that the reality would fall somewhere between the two scenarios.

Appendix 1

ICD10 Codes Mapping to WD02Z

Code	Code Description
A810	Creutzfeldt-Jakob disease
F000	Dementia in Alzheimer disease with early onset
F001	Dementia in Alzheimer disease with late onset
F002	Dementia in Alzheimer disease, atypical or mixed type
F009	Dementia in Alzheimer disease, unspecified
F010	Vascular dementia of acute onset
F011	Multi-infarct dementia
F012	Subcortical vascular dementia
F013	Mixed cortical and subcortical vascular dementia
F018	Other vascular dementia
F019	Vascular dementia, unspecified
F020	Dementia in Pick disease
F021	Dementia in Creutzfeldt-Jakob disease
F022	Dementia in Huntington disease
F023	Dementia in Parkinson disease
F024	Dementia in human immunodeficiency virus [HIV] disease
F028	Dementia in other specified diseases classified elsewhere
F03X	Unspecified dementia
G300	Alzheimer disease with early onset
G301	Alzheimer disease with late onset
G308	Other Alzheimer disease

G309 Alzheimer disease, unspecified

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Draft guidance comments form

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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):	Eisai

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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 Wednesday 20 November 2024. Please submit via NICE Docs.

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.	Not applicable
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	We are concerned there are inconsistencies in the EAG and NICE committee preferred assumptions in this appraisal and the ongoing appraisal of lecanemab [ID4043] in relation to apolipoprotein E ε4 (*APOE4*) testing costs. Lecanemab and donanemab are both indicated for the treatment of mild cognitive impairment and mild dementia due to Alzheimer's disease in adult patients that are

Please return to: **NICE DOCS**

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 Wednesday 20 November 2024. Please submit via NICE Docs.

	apolipoprotein E ε4 (*APOE4*) heterozygotes or non-carriers. Thus, testing for *APOE4* status should be performed prior to initiation of treatment using a validated test. Prior to testing patients should be appropriately counselled and consented according to national or local guidelines, as applicable.[1, 2] As such, this part of the diagnostic pathway is the same for both medicines and consistent approaches are expected to be applied in NHS practice; however the associated preferred assumptions differ in the NICE appraisals: • Donanemab: The EAG included the cost of the *APOE4* test (£44) and an outpatient consultant visit (£221.91) in their base case but did not include the cost of genetic counselling. Although the NICE committee decided the cost of an outpatient consultant visit should be included in their preferred assumptions, it is unclear if the cost of genetic counselling has also been included, as per EAG's clinical expert opinion (See donanemab EAG report, Section 4.2.11.4.3 Diagnostic and monitoring costs). • Lecanemab: The EAG aligned with the NHS England Alzheimer's MCI model costs and assumptions for *APOE4* testing, which includes the *APOE4* test cost (£250), an outpatient appointment (£200) and genetic counselling (£350) for 50% of *APOE4* homozygotes (See lecanemab EAG report, Table 4.18). In the donanemab appraisal the *APOE4* test is 5-6 fold lower than NHS England's APOE4 test cost (£250) and the outpatient visit and genetic counselling has not been consistently applied. References: [1] UK MHRA. Lecanemab final Summary of Product Characteristics (SmPC) [Internet]. 2024. Available from: https://mhraproducts4853.blob.core.windows.net/docs/ab479de5b0aa435befdb7d95cca47816c1a59759 [2] UK MHRA. Donanemab final Summary of Product Characteristics (SmPC) [Internet]. 2024. Available from: https://mhraproducts4853.blob.core.windows.net/docs/940882a3f371c1a69be326e3d993c1ec4582005e
2	We are concerned there are also inconsistencies in the EAG and NICE committee preferred assumptions in this appraisal and the ongoing appraisal of lecanemab [ID4043] in relation to on-treatment monitoring visits for disease progression to moderate Alzheimer's disease. Another similarity of the marketing authorisations for lecanemab and donanemab is the requirement to stop treatment if patients progress to moderate Alzheimer's disease though for donanemab, this is specifically before the end of the 18 months maximum treatment.[1, 2] However, the preferred assumptions for the frequency of outpatient consultation visits in clinical practice differ between the appraisals: • Donanemab: one consultation per model cycle (6-monthly) for the first 18-months. • Lecanemab: quarterly (3-monthly) outpatient review appointments as per the NHS England Alzheimer's MCI model. In the donanemab appraisal, the NICE committee concluded that there was uncertainty about whether additional on-treatment monitoring visits should be included and suggested further input from NHS England is required.

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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 Wednesday 20 November 2024. Please submit via NICE Docs.

	References: [1] UK MHRA. Lecanemab final Summary of Product Characteristics (SmPC) [Internet]. 2024. Available from: https://mhraproducts4853.blob.core.windows.net/docs/ab479de5b0aa435befdb7d95cca47816c1a59759 [2] UK MHRA. Donanemab final Summary of Product Characteristics (SmPC) [Internet]. 2024. Available from: https://mhraproducts4853.blob.core.windows.net/docs/940882a3f371c1a69be326e3d993c1ec4582005e

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.
- 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 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.

Please return to: **NICE DOCS**

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	PrescQIPP CIC
Location	
Conflict	No
Notes	
Comments on the DG:	

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

We note that the committee has asked for considerable additional information from both the submitting company and NHS England. We are therefore uncertain as to whether all the relevant evidence has been presented and taken into account.

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

We agree that the summaries are a reasonable interpretation of the evidence that has been considered thus far. However, we note the absence of a meta-analysis and associated sensitivity analysis which are required to enable a full interpretation of the evidence base.

We have significant concerns about the high degree of uncertainty in both the clinical evidence and economic modelling and analysis.

We have considerable concerns about the safety and efficacy of donanemab. Whilst the MHRA has granted a marketing authorisation in the UK, the CHMP are still considering the application and to date it has not been granted a license for use in the European Union.

Currently there is a lack of capacity and infrastructure in the NHS to ensure safe and equitable use of donanemab. Significant investment in NHS services including infrastructure, staffing and training would be required to support safe and effective use.

We agree that the marginal benefits demonstrated in clinical trials do not currently outweigh the costs to the NHS, and that a negative recommendation is appropriate at this time.

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

Yes

We agree that the marginal benefits demonstrated in clinical trials do not currently outweigh the costs to the NHS, and that a negative recommendation is appropriate 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 uncertainty in both the clinical evidence and economic modelling and analysis. A negative recommendation needs to stay in place until these issues have been resolved.

- **Section 1.1: Recommendations**

We strongly agree with the proposed negative NICE recommendation at this time.

There is considerable uncertainty within the clinical evidence and economic model, which has led the committee to make multiple requests for further information from the company and NHS England. Given this high level of uncertainty, we agree that donanemab should not be recommended.

There are significant concerns around safety and efficacy, and lack of capacity and infrastructure in the NHS to ensure safe and equitable implementation. We agree that the marginal benefits demonstrated in clinical trials do not currently outweigh the costs.

- **Section 3.4: Treatment positioning of donanemab**

The development of diagnostic and treatment pathways required for safe and effective use of donanemab will require significant time and investment.

Currently the NHS does not have sufficient capacity available in specialist monitoring services required for diagnosis, initiation and ongoing monitoring of treatment (MRI, PET-CT, lumbar puncture, genetic testing and counselling).

The patient pathway and clinical responsibility for diagnosis, treatment and for ongoing monitoring for patients treated with donanemab needs to be clear. Commissioning responsibility for providing care throughout the

patients journey needs be defined, with a joined up approach to providing services to ensure patient safety.

Availability of PET-CT scanners is variable across different locations in England. Provision of these services will need to be commissioned and funded at a national level to ensure equity in access for patients. This would take considerable time and investment. The availability of a blood test for amyloid beta in the future may make the use of donanemab a more cost effective and accessible treatment option.

There needs to be sufficient capacity within NHSE commissioned PET-CT scanning facilities for patients at both initiation and at follow up. Delay in available scans for individuals with moving amyloid plaques causing symptoms could make treatment decisions very difficult. There are significant patient safety concerns if the drug is continued when it should have been stopped.

Clarity on the service model and sector intended for administering donanemab is required. Appropriate consideration is needed around the resources required for staffing, training and infrastructure required for safe administration of donanemab. The drug is administered by I/V infusion over 1 hour as a 30-minute infusion followed by 30-minute observation, every 4 weeks. The guidance suggests the infusions would be given locally. Currently ICBs do not have the resources, infrastructure (including appropriate clinic space and the availability of emergency treatment for adverse drug reactions), or trained staff available to administer IV infusions in their mental health facilities. Likewise, existing infusion clinics providing a service in the acute setting do not have the capacity to provide a service on the scale required.

Local specialist centres for diagnosis, administration of treatment and monitoring need to be commissioned and funded at a national level to avoid variation in access to treatment and hence inequalities.

As this is a new and potentially large patient cohort, it could put considerable strain on already stretched mental health services. The impact on other mental health services users needs to be considered. There is a risk that incorporating this service into existing mental health services will adversely affect services to other mental health patients.

The impact of additional demand on specialised diagnostic service (MRI, PET-CT, lumbar puncture, genetic Testing) needs to be considered to ensure other patient groups are not unduly affected and disadvantaged including oncology, cardiology, and patients with other neurological conditions. Implementation of this TA could lead to increased demand and pressure on already challenged waiting lists for all treatment sectors. Robust assurance from NHSE, NICE and the current national contract holders for diagnostic scanning that they can meet the increased demand is required before this TA can be implemented.

- **Section 3.7: Clinical-effectiveness results**

We are concerned about the high level of uncertainty in the evidence for clinical effectiveness.

We note that in TRAILBLAZER-ALZ (phase 2), the difference in percentage decline in CDR-SB was not statistically significant, and this supports the committees' request for a meta-analysis.
In section 3.6 it is stated that iADRS is a newer outcome that is not well established in NHS practice. We are uncertain if this is an appropriate tool to use and how translatable clinical trial results will be to the real world setting.

There is a high degree of uncertainty of how the small change in CDR-SB demonstrated in the clinical trials translates to improvement in quality of life, and impact on health and social care services.

Professional bodies expressed mixed opinions on the clinical significance of the outcomes, further adding to the uncertainty of the benefits of treatment.

- **Section 3.8: Risks of bias**

We agree and are concerned about the potential for bias and support the committee's request for further sensitivity analysis based on a meta-analysis of the trial results.

- **Section 3.13: Long-term assumptions for full treatment effect**

There is considerable uncertainty over the long term effects of donanemab. The assumptions made regarding full treatment and waning effect have been made on the basis of modelling, and not on clinical trial data.

The company submission assumes that treatment will stop after 18 months, and there is currently no trial data beyond 18 months. Consequently the overall treatment effect and more specifically effect on overall disease outcome and prognosis remains unknown.

Any future positive NICE recommendations need to include clearly defined stopping criteria based on efficacy as well as safety. The draft guideline acknowledges that currently there are no clear guidelines on how progression to moderate disease is defined.

In the absence of clear unambiguous stopping criteria from NICE, systems will apply different review and stopping rules, and some patients and relatives will understandably want to continue the drug beyond the intended stop date. This will result in variation in access to treatment, and worsen health inequalities.

Clear, unambiguous review and stopping criteria using objective assessment of disease severity using validated tools currently in use in the

UK are required, to ensure that guidance is implemented consistently across all areas, and there is fair and equitable access for all patients.

It is vital that at the point treatment is initiated, patients and their relatives and carers understand that treatment will be stopped if the response to treatment does not meet pre-defined thresholds.

- **Section 3.14: Long-term assumptions for waning**

There is considerable uncertainty over the long term effects of donanemab. The assumptions made regarding full treatment and waning effect, have been made on the basis of modelling and not on trial data.

- **Section 3.17: Infusion costs**

We have significant concerns about the large variation in estimated infusion costs and it is unclear what figure was used in the health economic modelling. Clarity is needed on the care setting and service administering treatment, and an appropriate HRG cost used for financial modelling.

- **Section 3.18: Outpatient consultant visits**

We agree that further assessment of the psychological impact of APOE4 testing is needed, along with the need for genetic counselling. Clarity is needed regarding the pathway to ensure that services are appropriately designed and cost impact can be accurately assessed.

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

- **Section 3.2: Diagnosing mild cognitive impairment and mild dementia caused by Alzheimer's disease**

“The clinical experts emphasised that all people with mild cognitive impairment caused by Alzheimer's disease eventually progress to having dementia.”

This statement is incorrect and should be amended. I wonder if it is a simple transcription error and should read "...experts emphasised that NOT all people with mild cognitive impairment caused by Alzheimer's disease eventually progress to having dementia."

Many people with PET or CSF evidence of amyloid pathology and MCI will never go on to develop clinical dementia. 54-59% of amnestic MCI patients with a positive amyloid test had not progressed to dementia after 3 years (Wolk (2018), Vos (2015)). In post mortem studies 20-39% of cognitively normal older people had amyloid pathology in the brain at death, but had never developed dementia (Boyle (2024), Bowles (2019), Robinson (2018), Schneider (2009)). In people with MCI and a positive amyloid test many other possible contributing factors may increase or decrease their risk of progression to dementia. These contributing factors include vascular disease, poor sleep, poor hearing, low mood, drug effects, non-degenerative brain ageing, and metabolic effects of diabetes. Similarly, there are many factors that may confer resilience to progression of MCI, even in people with amyloid positivity, including social class, level of educational attainment, genetic resilience, high levels of social interaction and support, good cardiac health, and good nutrition. Many of these factors affecting both risk of progression and resilience are modifiable, and people with MCI may have, or may develop, sufficient resilience to further neuro-degeneration such that they never progress from MCI to dementia, even when there is on-going amyloid deposition in the brain.

Bowles E, Crane P, Walker R, Chubak J, LaCroix A, Anderson M, et al. Cognitive Resilience to Alzheimer's Disease Pathology in the Human Brain. JOURNAL OF ALZHEIMERS DISEASE. 2019;68:1071-83.

Boyle R, Townsend D, Klinger H, Scanlon C, Yuan Z, Coughlan G, et al. Identifying longitudinal cognitive resilience from cross-sectional amyloid, tau, and neurodegeneration. ALZHEIMERS RESEARCH & THERAPY. 2024;16.

Robinson J, Corrada M, Kovacs G, Dominique M, Caswell C, Xie S, et al. Non-Alzheimer's contributions to dementia and cognitive resilience in The 90+Study. ACTA NEUROPATHOLOGICA. 2018;136:377-88.

Schneider J, Aggarwal N, Barnes L, Boyle P, Bennett D. The Neuropathology of Older Persons with and Without Dementia from Community versus Clinic Cohorts. JOURNAL OF ALZHEIMERS DISEASE. 2009;18:691-701.

Vos S, Verhey F, Frölich L, Kornhuber J, Wiltfang J, Maier W, et al. Prevalence and prognosis of Alzheimer's disease at the mild cognitive impairment stage. BRAIN. 2015;138:1327-38.

Wolk D, Sadowsky C, Safirstein B, Rinne J, Duara R, Perry R, et al. Use of Flutemetamol F18-Labeled Positron Emission Tomography and Other Biomarkers to Assess Risk of Clinical Progression in Patients With Amnestic Mild Cognitive Impairment. Jama Neurology. 2018;75(9):1114-23.

Name	[redacted]
Role	
Other role	
Organisation	NHS BSW ICB
Location	
Conflict	No
Notes	
Comments on the DG:	

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

We note that the committee has asked for considerable additional information from both the submitting company and NHS England. We are therefore uncertain as to whether all the relevant evidence has been presented and taken into account.

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

We agree that the summaries are a reasonable interpretation of the evidence that has been considered thus far. However, we note the absence of a meta-analysis and associated sensitivity analysis which are required to enable a full interpretation of the evidence base.

We have significant concerns about the high degree of uncertainties in both the clinical evidence and economic modelling and analysis.

We have considerable concerns about the safety and efficacy of donanemab. Whilst the MHRA has granted a marketing authorisation in the UK, the CHMP are still considering the application and to date it has not been granted a license for use in the European Union.

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We agree that the marginal benefits demonstrated in clinical trials do not currently outweigh the costs to the NHS, and that a negative recommendation is appropriate at this time.

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

Yes

We agree that the marginal benefits demonstrated in clinical trials do not currently outweigh the costs to the NHS, and that a negative recommendation is appropriate 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 age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?**

None known

- **Section 1.1: Recommendations**

“Donanemab is not recommended, within its marketing authorisation, for treating mild cognitive impairment and mild dementia due to Alzheimer's disease in adults who are apolipoprotein (APO) E4 heterozygotes or non-carriers.”

We strongly agree with the proposed negative NICE recommendation at this time.

There is considerable uncertainty within the clinical evidence and economic model, which has led the committee to make multiple requests for further information from the company and NHS England. Given this high level of uncertainty, we agree that donanemab should not be recommended.

- **Section 3.4: Treatment positioning of donanemab**

The development of diagnostic and treatment pathways required for safe and effective use of donanemab will require significant time and investment.

Currently the NHS does not have sufficient capacity available in specialist monitoring services required for diagnosis, initiation and ongoing monitoring of treatment (MRI, PET-CT, lumbar puncture, genetic testing and counselling).

The patient pathway and clinical responsibility for diagnosis, treatment and for ongoing monitoring for patients treated with donanemab needs to be clear. Commissioning responsibility for providing care throughout the

patients journey needs be defined, with a joined up approach to providing services to ensure patient safety.

Availability of PET-CT scanners is variable across different locations in England. Provision of these services will need to be commissioned and funded at a national level to ensure equity in access for patients. This would take considerable time and investment. The availability of a blood test for amyloid beta in the future may make the use of donanemab a more cost effective and accessible treatment option.

There needs to be sufficient capacity within NHSE commissioned PET-CT scanning facilities for patients at both initiation and at follow up. Delay in available scans for individuals with moving amyloid plaques causing symptoms could make treatment decisions very difficult. There are significant patient safety concerns if the drug is continued when it should have been stopped.

Clarity on the service model and sector intended for administering donanemab is required. Appropriate consideration is needed around the resources required for staffing, training and infrastructure required for safe administration of donanemab. The drug is administered by I/V infusion over 1 hour as a 30-minute infusion followed by 30-minute observation, every 4 weeks. The guidance suggests the infusions would be given locally. Currently ICBs do not have the resources, infrastructure (including appropriate clinic space and the availability of emergency treatment for adverse drug reactions), or trained staff available to administer IV infusions in their mental health facilities. Likewise, existing infusion clinics providing a service in the acute setting do not have the capacity to provide a service on the scale required.

Local specialist centres for diagnosis, administration of treatment and monitoring need to be commissioned and funded at a national level to avoid variation in access to treatment and hence inequalities.

As this is a new and potentially large patient cohort, it could put considerable strain on already stretched mental health services. The impact on other mental health services users needs to be considered. There is a risk that incorporating this service into existing mental health services will adversely affect services to other mental health patients.

The impact of additional demand on specialised diagnostic service (MRI, PET-CT, lumbar puncture, genetic Testing) needs to be considered to ensure other patient groups are not unduly affected and disadvantaged including oncology, cardiology, and patients with other neurological conditions. Implementation of this TA could lead to increased demand and pressure on already challenged waiting lists for all treatment sectors. Robust assurance from NHSE, NICE and the current national contract holders for diagnostic scanning that they can meet the increased demand is required before this TA can be implemented.

- **Section 3.7: Clinical-effectiveness results**

We are concerned about the high level of uncertainty in the evidence for clinical effectiveness.

We note that in TRAILBLAZER-ALZ (phase 2), the difference in percentage decline in CDR-SB was not statistically significant, and this supports the committees' request for a meta-analysis.

In section 3.6 it is stated that iADRS is a newer outcome that is not well established in NHS practice. We are uncertain if this is an appropriate tool to use and how translatable clinical trial results will be to the real world setting.

There is a high degree of uncertainty of how the small change in CDR-SB demonstrated in the clinical trials translates to improvement in quality of life, and impact on health and social care services.

Professional bodies expressed mixed opinions on the clinical significance of the outcomes, further adding to the uncertainty of the benefits of treatment.

- **Section 3.8: Risks of bias**

We agree and are concerned about the potential for bias and support the committee's request for further sensitivity analysis based on a meta-analysis of the trial results.

- **3.13 Long-term assumptions for full treatment effect**

There is considerable uncertainty over the long term effects of donanemab. The assumptions made regarding full treatment and waning effect have been made on the bases of modelling, and not on clinical trial data.

The company submission assumes that treatment will stop after 18 months, and there is currently no trial data beyond 18 months. Consequently the overall treatment effect and more specifically effect on overall disease outcome and prognosis remains unknown.

Any future positive NICE recommendations need to include clearly defined stopping criteria based on efficacy as well as safety. The draft guideline acknowledges that currently there are no clear guidelines on how progression to moderate disease is defined.

In the absence of clear unambiguous stopping criteria from NICE, systems will apply different review and stopping rules, and some patients and relatives will understandably want to continue the drug beyond the intended stop date. This will result in variation in access to treatment, and worsen health inequalities.

Clear, unambiguous review and stopping criteria using objective assessment of disease severity using validated tools currently in use in the UK are

required, to ensure that guidance is implemented consistently across all areas, and there is fair and equitable access for all patients.

It is vital that at the point treatment is initiated, patients and their relatives and carers understand that treatment will be stopped if the response to treatment does not meet pre-defined thresholds.

- **3.14 Long-term assumptions for waning**

There is considerable uncertainty over the long term effects of donanemab. The assumptions made regarding full treatment and waning effect, have been made on the basis of modelling and not on trial data

- **Section 3.17: Infusion costs**

We have significant concerns about the large variation in estimated infusion costs and it is unclear what figure was used in the health economic modelling. Clarity is needed on the care setting and service administering treatment, and an appropriate HRG cost used for financial modelling.

- **Section 3.18 Outpatient consultant visits**

The EAG advised the company's estimates for the diagnosis and monitoring of people with early Alzheimer's disease were broadly reasonable. The EAG's clinical experts agreed except for the costing of APOE4 testing, which included the test (£44) but not the cost of an outpatient appointment (£222). The EAG's clinical experts suggested that most carriers of an APOE4 allele would also need some counselling because genetic results are difficult to understand and should be explained to people even if they are not eligible for treatment. One of the EAG's experts said that counselling could be part of a normal outpatient appointment already planned as part of the diagnostic process. The EAG did not include a counselling appointment in its base case but explored it as part of a scenario based on submissions from NHS England. The EAG noted that patients do not have outpatient consultant visits for monitoring in the model. At clarification, the company included the option to include 1 outpatient consultant visit per cycle in its model and provided a scenario analysis including this. It explained that it did not adjust its base case because it expected outpatient consultant visits to be covered by the NHS Reference costs included in the model. The EAG disagreed and advised that these needed to be costed separately. So, the EAG added 1 outpatient consultant visit at diagnosis and 1 per cycle during treatment (3 over 18 months) to its base case. The committee noted that the EAG's approach was informed by clinical expert advice. It decided that the cost of an outpatient consultant visit should be included for all people having APOE4 testing. It concluded that there was uncertainty about whether additional on-treatment monitoring visits should be included and this requires further clinical input, including from NHS England."

We agree that further assessment of the psychological impact of APOE4 testing is needed, along with the need for genetic counselling. Clarity is

needed regarding the pathway to ensure that services are appropriately designed and cost impact can be accurately assessed.

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

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

The second meeting to assess the view of experts, evidence and those affected is very welcome. The views of carers and sufferers are present but I do not believe that the Committee has enough input from carers to arrive at this decision.

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

Given the way in which the the drug is delivered by infusion this clearly adds to the cost of delivery. However, another major part of the cost is scanning and with the pressure on diagnostic scanning equipment already, it feels like AD sufferers are bearing the brunt of an inadequate policy on scanning infrastructure at the very time when a new dawn is breaking on beating AD. It is no surprise that a further burden on scanner wait lists by allowing this drug to be available along with the attendant scanning requirement is undesirable. We simply don't have the infrastructure to facilitate this and it would be best to be honest with the public that this is part of the consideration.

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

No - the costs/benefits in terms of quality of life for sufferer and carer, care home and end of life care savings are not clear and wider picture has largely been ignored. This is a pathfinder drug and if made available to those with a diagnosis of MCI it has the potential to lessen calls on the NHS's resources. As only a small percentage of those who have dementia/AD have had the gold standard diagnostic and diagnosis. this might be a relatively small group in the coming 2-3 years. Mike has had detailed memory testing, MRI scan and Lumbar puncture largely because of unrelenting pressure to get a diagnosis, our relative youth and experience and using savings and the private health route for some of it has got us to this stage. Timely diagnosis meant access to currently available

medications sooner, some help in terms of blue badge etc., emotional certainty to start to come to terms with the presence of chronic illness in the family, the ability to create a support network sooner and a better quality of life than others in the same boat but with less ability to move things along in the same way that we have. People like Mike are willing to help the NHS for future generations. My experience of navigating this over the last three years has been very poor and whilst we have had some good support from parts of the NHS, I hate to think how others who are much older or less well versed fare - I can only assume not well. The recommendations in isolation may be seen as sound and a suitable basis for guidance to the NHS but the wider picture cannot be ignored. After all we all live in both the narrow and the wider picture.

- **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 age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?**

As this affects mostly older people I believe that the age discrimination is at play here.

- **Section 1: Recommendations - Why the committee made these recommendations**

"Not enough evidence on the long term effects of donenamab"

Give those with early symptoms the drug and then they can benefit from the slower rate of decline and help provide the evidence base for future generations. Given the first phase of AD is pre-clinicial (before symptoms are seen) this is vital if we help the next generation of potential sufferers – people who are now in their 40s. When cheaper diagnostics arrive for eg blood test the ability to screen pre symptoms and treat with these drugs (when cheaper) could improve the lives of millions plus millions (sufferer and carer) and save millions in care home fees. Living bed bound or without any mental capacity with double incontinence is a terrifying sight. I know I saw it. Given Mike's youth and otherwise excellent health this is a terrifying final prospect for a man, who like my father, was otherwise fit and well.

Bullet point 3: how long the effects of donanemab last after stopping treatment

People like Mike don't have time to wait until this is further tested. If you give it to him and others with MCI we can help this be determined, or not, over the next 2 years, they will gain a little more life worth living than are likely to have, and care home admission delayed even by a year or two.

Bullet point 4: the health-related quality of life of people living with mild cognitive impairment and mild dementia caused by Alzheimer's disease and their carers

The trial proved a reported slowing of the decline v the placebo. If Mike continues to decline at the rate of the last 3 years I believe he will have lost many more of executive skills eg dressing, remembering to shower, making a cup of tea etc. These are small things but if you cannot do it, when you used to have a staff of 300 and write multimillion pound funding bids to the EU only a few years ago and you are only 66, it is very sad.
As AD has a pre clinical incubation of 10-15 years before symptoms show people like Mike will be helping a pathway toward medications that might help those in their 30, 40s and 50s now. In the same way that cholesterol medication has had a huge impact. We must start now! My father was diagnosed and told there is nothing that can be done - here we are 22 years later with the same message.

AD is well understood to be the hardest chronic illness to live with and one of the most feared. I am a lay person and although I cannot comment on the clinical and technical findings I still want my voice heard in these deliberations. I have read the consultation documentation including the minutes and presentations from the Technology Approval Committee on the 3rd July 2024, and have an appreciation now of the complexity of NICE's task in considering the use of medications with in NHS. I have learnt a new word that applies to me - "disutility". I have sympathies for those attempting to arrive at potentially life changing decisions for large numbers of the population, this is important work that largely goes unseen by the public at large. What I can comment on here, I do so in my capacity as a citizen and a carer. What I can offer is a detailed lived experience and knowledge of the system around those with dementia. My experience, whilst there are a few bright spots and a few key individuals, shows that the system is broken and bitterly failing those with dementia. I can comment on a span of challenging topics from navigating access to drug trials and how medications are being developed, the challenges and pace of diagnosis, the inadequacy of follow up and lack of integrated care, inadequacy of memory clinics, misinterpretation of MRI scans and challenges for carers support. Whilst this wide range of topics are not the scope for this discussion on reading the paperwork and findings I believe that the voice of carers and sufferers has not been heard sufficiently. There are compelling comments from carers and sufferers at the start of the power point presentation dated 3rd July 2024 but these do not travel through to the rest of the discussion or reflect in the recommendations. I have views as to why that is and some of them are echoed in the equality considerations mentioned on page 12 and 13 of the powerpoint presentation.
I am 60 year old carer for my husband who was diagnosed with Alzheimers 3 years ago aged 63. I have a lived experience of the devastation caused by AD to both the carer and the sufferer because of the last three years, as well as from watching my parents as my father was diagnosed with AD at

age 68 and died after a long battle 5 years ago. I saw his slow and heart-breaking decline and the impact on my late mother.

This is the second drug now licenced by the MHRA, deemed safe and effective, and yet in spite of the fact that according the NICE dementia is the leading cause of death in the UK it will be unavailable to those at the early stages of dementia, largely on costs ground. This is in spite of the fact the evidence shows that in the case of Donanemab the indications are that the drug can be stopped after 12-18 months and after week 76 76% of people treated with Donanemab had amyloid clearance. Amyloid is widely held as the most likely cause of AD.

This is a pioneering drug with inevitably high up front costs given the cost of infusion delivery and ongoing diagnostic scanning but the economics of potential savings on care home, hospice, and carer costs further down the line apparently don't stack up.

Experts call these pioneer drugs "the beginning of the end" for eradicating AD. As part of the battle to look for a cure for AD we feel that strong consideration must be given to allowing those with an early AD/MCI diagnosis to participate in an NHS backed study. In the three years since Mike's diagnosis he has already lost key executive skills. The opportunity to slow the progression is incredible, but unavailable to us. If we lived in the USA that would not be the case. This is a double heartbreak watching the person you love lose independence and for me, the carer, having to become 2 minds. If the drug could stave off 2/3 years at end of life in a care home the cost of the drug would be similar. Mike is just like you and me and worked as a public servant for 43 years until he retired and received this diagnosis. He has never been sick and never called on the NHS. We need our NHS now as we do not have the luxury of time to wait. If the drug is not available to him now his and my future is sealed. This disease has blighted two lives and the kind of end of life my father endured seems an inevitability if we cannot access this drug.

I appreciate these comments are not technical and may be considered emotional so I am grateful for them being read.

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

I am just an individual who is passionate about getting this drug passed by NICE for use on the NHS.

1:People with early Alzheimer's need to be given a chance to this second (the first has already been refused by NICE) major breakthrough drug. They need to be given hope and a choice to have this drug.

2:This drug is a huge breakthrough for people with early stage Alzheimer's, why isn't it being given a chance? Dementia costs the UK £42 billion pounds. Spending on diagnosis and treatment is equivalent to just 1.4% of this. This to me is enough of a reason to invest in this breakthrough drug.

3. I have compared a new cancer drug that has recently come out on the NHS. It seems to be pretty expensive with little proof yet that it works. This drug is used after all the other costly treatment involved. Obviously I am happy about this drug but what is the difference to giving Donanemab a try, a drug that is a major breakthrough. It can only be improved if we get this ball rolling.

4. The new blood test that is mentioned to diagnose Alzheimer's is available. It could surely be made available alongside the start of the treatment. The treatment wouldn't be given out to a huge number of people to start. As they would be in early stages, then surely the positive outcome outweighs the cost of what the disease would cost in later stages if the treatment isn't given. Also, and mainly, the quality of life the person and family would benefit from the treatment.

5. Any drug has a risk of death, this one is handled well and with MRI scans for risk of ARIA.

6. I have read several personal stories of people on drug trials for this drug in the US and UK. The outcome for them has always seemed positive.
I could go on more and I know I haven't filled in all the forms. However I do have what I consider a good understanding of Alzheimer's and this drug. It just leaves me flabbergasted as to why this isn't being the go ahead for the NHS. Heartbreaking for so many.

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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 the Draft guidance document.

Produced by	**Southampton Health Technology Assessments Centre (SHTAC)**
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Date completed	13/12/2024

[redacted]

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LIST OF ABBREVIATIONS

AE	Adverse event
APOE ε4	Apolipoprotein E ε4
ARIA	Amyloid-related imaging abnormality
ARIA-E	Amyloid-related imaging abnormality of oedema/effusions
ARIA-H	Amyloid-related imaging abnormality of microhaemorrhages/hemosiderin deposits
CAA	Cerebral Amyloid angiopathy
CDR-SB	Clinical Dementia Rating Sum of Boxes
CI	Confidence interval
CIC	Commercial in confidence
CL	Centiloids
CS	Company submission
DGD	Draft guidance document
EAG	External Assessment Group
HRQoL	Health-related quality of life
iADRS	Integrated Alzheimer's Disease Rating Scale
ICER	Incremental cost-effectiveness ratio
LSM	Least-squares mean;
MHRA	Medicines and Healthcare products Regulatory Agency
MMRM	Mixed models for repeated measures
MRI	Magnetic resonance imaging
NCS2	Natural cubic spline with 2 degrees of freedom
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NR	Not reported
PAS	Patient access scheme
PET	Positron emission tomography
PSA	Probabilistic sensitivity analysis
QALY	Quality-adjusted life year
RCT	Randomised controlled trial
SD	Standard deviation
SE	Standard error
SmPC	Summary of Product Characteristics

SUVR	Standardised uptake value ratio
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 the NICE's draft guidance document (issue date October 2024) for the technology appraisal on 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 21st November 2024.

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 on donanemab for treating mild cognitive impairment or mild dementia caused by Alzheimer's disease 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 (DGD) with the numbered comments in the company's draft guidance response form.[1]

2.1 Comment 1: Update to marketing authorisation

In the original company submission (CS), UK regulatory approval had not yet been granted and therefore the CS was based on the anticipated marketing authorisation wording for donanemab (shown in Table 1 in the company's response to draft guidance). UK marketing authorisation was granted on 23 October 2024[2] and the confirmed indication wording is: "Donanemab is indicated for the treatment of mild cognitive impairment and mild dementia due to Alzheimer's disease (AD) in adult patients that are apolipoprotein E ε4 (APOE ε4) heterozygotes or non-carriers". In addition, the Summary of Product Characteristics[2] (SmPC) sets out additional requirements, some of which further impact the patient population eligible to receive donanemab and other aspects which are important for the health economic model:

- Testing for APOE ε4 status should occur before the initiation of treatment and prior to testing patients should be appropriately counselled and consented. As per the confirmed indication wording, people who are APOE ε4 heterozygotes or non-carriers are potentially eligible for treatment but those who are APOE ε4 homozygotes are not.
- If a patient progresses to moderate Alzheimer's disease before the end of the 18 months maximum treatment, donanemab should be stopped. We note that the SmPC does not specify a test or tests that should be used to determine that a patient has progressed to moderate Alzheimer's disease.
- A recent brain magnetic resonance imaging (MRI) (within 1 year) image should be obtained prior to initiating treatment. An MRI should also be performed prior to the second donanemab dose, prior to a dose increase, and prior to the seventh donanemab dose. Additional MRIs may be considered if clinically indicated and are required in the case of amyloid-related imaging abnormality of oedema/effusions (ARIA-E) or amyloid-related imaging abnormality of microhaemorrhages/hemosiderin deposits (ARIA-H), as set out in the SmPC.
- Section 4.3 of the SmPC lists the contraindications to donanemab treatment and these include (but are not limited to): imaging findings suggestive of Cerebral Amyloid Angiopathy (CAA) that increase the risk of amyloid-related imaging

abnormality (ARIA) or intracerebral haemorrhage; treatment with donanemab should not be initiated in patients receiving ongoing anticoagulant therapy.

2.2 Comment 2: Additional estimates from TRAILBLAZER-AZ 2 and from the meta-analyses of TRAILBLAZER-ALZ 2 and TRAILBLAZER-ALZ for CDR-SB and iADRS for the UK eligible population and by APOE4 status

2.2.1 Additional estimates from TRAILBLAZER-ALZ 2

The company provided updated clinical data from TRAILBLAZER-ALZ 2 in the relevant patient population in line with the final marketing authorisation. The company has not indicated how many participants have been excluded from the analysis because they would not be eligible for donanemab treatment in the UK. Table 2 in the company's response to the draft guidance provides the numbers contributing data to each analysis for the clinical outcomes of the Integrated Alzheimer's Disease Rating Scale (iADRS) and the Clinical Dementia Rating Sum of Boxes (CDR-SB) and Table 4 in the SmPC provides the numbers in each group for the indicated population but the values provided for the outcomes are not identical, as shown below in Table 1. It is unclear whether these differences are due to different numbers in the analyses or differences in the methods used for the analyses. The differences do not alter the overall conclusions.

Table 1 TRAILBLAZER-ALZ 2: comparison of iADRS and CDR-SB outcomes reported in the company response to draft guidance and the donanemab SmPC

Outcome	UK eligible population (Reported in company draft guidance response[1])		Indicated population (Reported in SmPC[2])	
	Donanemab (N=NR)	Placebo (N=NR)	Donanemab (N=717)	Placebo (N=730)
iADRS (NCS2)	[redacted]	[redacted]	N=NR	N=NR
Mean (SD) baseline	[redacted]	[redacted]	104.66 (NR)	103.83 (NR)
Change from baseline[a]	[redacted][b]	[redacted][b]	-10.21 (NR)	-13.59 (NR)
Difference from placebo (95% CI)[a]	[redacted][b]		3.38 (1.83, 4.92)	-
p-value	[redacted]		P<0.0001	
CDR-SB (MMRM)	[redacted]	[redacted]	N=NR	N=NR
Mean (SD) baseline	[redacted]	[redacted]	3.96 (NR)	3.94 (NR)

Outcome	UK eligible population (Reported in company draft guidance response[1])		Indicated population (Reported in SmPC[2])	
	Donanemab (N=NR)	Placebo (N=NR)	Donanemab (N=717)	Placebo (N=730)
Change from baseline	[redacted]	[redacted]	1.67 (NR)	2.43 (NR)
Difference from placebo (95% CI)	[redacted]		-0.77 (-1.04, -0.49)	-
p-value	[redacted]		P<0.0001	

Source: Results for the UK eligible population taken from Table 2 in the company response to draft guidance. Results for the indicated population taken from Table 4 in the SmPC for donanemab[2]
CDR-SB, sum of boxes of the Clinical Dementia Rating Scale; CI, confidence interval; iADRS, Integrated Alzheimer Disease Rating Scale; LSM, least-squares mean; MMRM, mixed models for repeated measures; NCS2, natural cubic spline with 2 degrees of freedom; NR, not reported; SD, standard deviation.
[a] Table 2 in the company response to draft guidance indicates least-squares mean (LSM) with 95% CI is reported but there is only one value provided, not a range.
[b] Table 2 in the company response to draft guidance specifies that LSM change and LSM difference versus placebo are reported.

In comparison to the results presented for the whole TRAILBLAZER-ALZ 2 trial, the results for the UK eligible population in terms of slowing of clinical progression for the iADRS and CDR-SB show [redacted] (Table 2).

Table 2 Comparison of iADRS and CDR-SB outcomes for the TRAILBLAZER-ALZ 2 total population and the UK eligible population

Outcome [a]	Statistical method	Donanemab			Placebo			LSM difference vs placebo (95% CI)	p value vs placebo	Slowing of clinical progression % (95% CI)[b]
		Mean (SD)		LSM change (95% CI)	Mean (SD)		LSM change (95% CI)			
		Baseline	76 Weeks		Baseline	76 Weeks				
Total TRAILBLAZER-ALZ-2 population										
iADRS		n=775	n=583		n=824	n=653				
	NCS2[c]	104.55 (13.90)	96.98 (20.87)	−10.19 (−11.22, −9.16)	103.82 (13.88)	93.82 (20.38)	−13.11 (−14.10, −12.13)	2.92 (1.51, 4.33)	<0.001	22.3 (11.38, 33.15)
	MMRM[d]	104.55 (13.90)	96.98 (20.87)	−10.19 (−11.27, −9.11)	103.82 (13.88)	93.82 (20.38)	−13.22 (−14.27, −12.18)	3.03 (1.60, 4.47)	<0.001	22.9 (11.96, 33.92)
CDR-SB		n=794	n=598		n=838	n=672				
	NCS2	3.92 (2.06)	5.25 (3.21)	1.66 (1.48, 1.83)	3.89 (2.03)	5.80 (3.22)	2.33 (2.16, 2.50)	−0.67 (−0.92, −0.43)	<0.001	28.9 (18.26, 39.53)
	MMRM[c,d]	3.92 (2.06)	5.25 (3.21)	1.72 (1.53, 1.91)	3.89 (2.03)	5.80 (3.22)	2.42 (2.24, 2.60)	−0.70 (−0.95, −0.45)	<0.001	28.9 (18.41, 39.44)
UK eligible population TRAILBLAZER-ALZ-2										
iADRS		[redacted]								
	NCS2								<.001	
	MMRM[d]								<0.0001	
CDR-SB										
	NCS2								<.001	
	MMRM[d]								<0.0001	

Source: Results for the total TRAILBLAZER-ALZ 2 population come from CS Table 11 which in turn gives the source as Sims et al. (2023).[3] Results for the UK eligible population from TRAILBLAZER-ALZ 2 come from Table 2 in the company response to draft guidance.[1]
CDR-SB, Clinical Dementia Rating Sum of Boxes; CI, Confidence interval; iADRS, Integrated Alzheimer's Disease Rating Scale; LSM, Least-squares mean; MMRM, Mixed-effect model for repeated measures; NCS2, Natural cubic spline model with 2 degrees of freedom; SD, Standard deviation.

[a] Clinical outcomes were scored as follows: CDR-SB range from 0 to 18, with higher scores indicating greater clinical impairment; iADRS range from 0 to 144, with lower scores indicating greater impairment.
[b] The percentage of slowing of clinical progression was calculated by dividing the LSM change from baseline treatment differences at 76 weeks by the LSM change from baseline with placebo at 76 weeks and multiplying by 100. The CI was estimated using the Delta method.
[c] Gated outcome, also indicated via grey shaded cells.
[d] For MMRM analyses, 95%CIs for LSM changes were calculated with the normal approximation method.

2.2.2 Meta-analyses of TRAILBLAZER-ALZ 2 and TRAILBLAZER-ALZ for CDR-SB and iADRS

Although the company state they have performed a meta-analysis, from the information provided we believe that the data from the two trials have been combined by simple pooling without being weighted. It would have been helpful to see a visual representation (i.e. a forest plot) showing the data for each trial separately and the weighted pooled estimate after meta-analysis of the two trials. Any heterogeneity could have been addressed by use of a random-effects model.

The company have provided the results of analyses pooling individual data from the TRAILBLAZER-ALZ 2 and TRAILBLAZER-ALZ trials for the participants who correspond to the UK eligible population as described in the donanemab marketing authorisation (i.e. excluding APOE ε4 homozygotes patients, patients with missing APOE4 status, and patients with anticoagulants). The company do not state how many trial participants contribute data to the analyses of the two outcomes considered, CDR-SB and iADRS. The same Cox proportional hazard model that was used to estimate the hazard ratio of disease progression for TRAILBLAZER-ALZ 2 in the original CS, as summarised in our original EAG report in section 3.2.5.3, is used. The same definitions for clinical worsening are also used. The company added a study variable to their Cox proportional hazard model and ran the model with the interaction study*study treatment. As this interaction was not statistically significant (p=0.2137 for CDR-SB and p=0.8326 for iADRS), the interaction was removed from the model. The company reports hazard ratios for the CDR-SB and iADRS for four new analyses which are shown alongside the results from the original analysis for the total TRAILBLAZER-ALZ 2 population in Table 5 of the company response to draft guidance. For the CDR-SB, the original result for the overall TRAILBLAZER-ALZ 2 population was a hazard ratio of 0.623, and the hazard ratios from the four new analyses range from [redacted]. For the iADRS, the original result for the overall TRAILBLAZER-ALZ 2 population was a hazard ratio of 0.700, and the hazard ratios from the four new analyses range from [redacted]. The results of the new analyses are reasonably consistent with the results of the original analysis (also see our response to company comment 13 in section 2.13 of this document). The company do not report the hazard ratios for the CDR-SB and iADRS for the UK eligible population from TRAILBLAZER-ALZ alone.

In Table 7 of the company response to draft guidance the company presents iADRS and CDR-SB outcomes from baseline to 76 weeks for the UK eligible population for the TRAILBLAZER-ALZ 2 and TRAILBLAZER-ALZ trials combined. The company state that these data were obtained using the same models as previously described for

TRAILBLAZER-ALZ 2 with the addition of the study variable as a covariate. In comparison to the total TRAILBLAZER-ALZ-2 population and the UK eligible population from TRAILBLAZER-ALZ-2 (presented in Table 2 above), the analyses of the combined TRAILBLAZER-ALZ-2 and TRAILBLAZER-ALZ trials for the UK eligible population show [redacted] slowing of clinical progression, except for the CDR-SB MMRM analysis where the slowing of clinical progression [redacted] as for the UK eligible population of TRAILBLAZER 2. However, differences between the results from the analysis of the combined TRAILBLAZER-ALZ-2 and TRAILBLAZER-ALZ trials for the UK eligible population and the results shown in Table 2 are small (ranging between [redacted] and [redacted] percentage points).

The company reiterate their concerns about some differences between the TRAILBLAZER-ALZ 2 and TRAILBLAZER ALZ trials (we summarised the EAG view on the differences in sections 3.2.1, Table 7 and 3.4 of our original report) and state that the outcome of the meta-analysis of the trials should be interpreted with caution. As noted above we believe that any heterogeneity could have been addressed in a random-effects meta-analysis.

Our clinical experts agreed that the minor differences between trials would be unlikely to have an impact on trial outcomes and it is our belief that participants from both TRAILBLAZER-ALZ 2 and TRAILBLAZER ALZ would be treated in the NHS providing they meet the licenced indication in the donanemab SmPC. Therefore, our preference is to use the hazard ratio from the pooled data of TRAILBLAZER-ALZ 2 and TRAILBLAZER-ALZ UK eligible population (HR= [redacted]) in the economic model.

2.2.3 Additional estimates by APOE ε4 status

Subgroup effects by APOE ε4 allele status were considered by the NICE evaluation committee at the meeting which was held before the full details of the marketing authorisation for donanemab were known. We had raised the impact of APOE ε4 allele status as a key issue (Key Issue 5 in the original EAG report) because people homozygous for the APOE ε4 allele had a greater risk of experiencing ARIA events than people heterozygous for this allele and both subgroups had a greater risk than non-carriers. Additionally, subgroup analyses of the iADRS and CDR-SB at 76 weeks from the TRAILBLAZER-ALZ 2 trial hinted at potential differences in clinical response by APOE ε4 allele status. Now that the details of the marketing authorisation are known, only people who are APOE ε4 heterozygotes or non-carriers are eligible for treatment and consequently these are the two subgroups that the company focuses on.

In their response to the draft guidance, the company investigated the impact of APOE ε4 allele status on disease progression as measured by the CDR-SB and iADRS scales by

incorporating the variable for APOE ε4 allele status and its interaction with study treatment into the same Cox proportional model described above in section 2.2.2. The company presents results in Table 8 of their response for non-carriers and heterozygotes for the APOE ε4 allele in both the TRAILBLAZER-ALZ 2 UK eligible population and the combined TRAILBLAZER-ALZ 2 and TRAILBLAZER-ALZ UK eligible population. The company does not report how many trial participants contribute data to these analyses. This analysis showed the number of APOE ε4 alleles by study treatment interaction was not statistically significant for either of the two outcomes considered (no p-values reported). Similarly, the company state that they found no evidence that APOE ε4 status (non-carrier versus heterozygous patient) was a treatment effect modifier when they conducted their NCS2 analyses and MMRM analyses for the least-squares mean change from baseline at Week 76 differences between placebo and donanemab by APOE ε4 status (results reported in Table 9 and Table 10 respectively of the company response to draft guidance). The EAG has no further comment on this issue.

2.3 Comment 3: Treatment stopping rule at 18 months as informed by monitoring of amyloid clearance

In their original submission, the company assumed that 10% of patients would follow a treat-to-clear strategy as informed by amyloid clearance detected on amyloid-positron emission tomography (PET) imaging. The EAG, based on the limited capacity of the UK health system in terms of PET scan infrastructure informed by the EAG's clinical experts, assumed that all patients would have a fixed treatment duration of 18 months (except if other stopping rules applied). The committee requested further information from the company that fully explained the estimated proportion of people who stop donanemab before 18 months based on amyloid-PET scan results.

The company provided additional arguments, such as: (1) the use of donanemab is expected within specialist sites that already have PET scanning capability and the necessary infrastructure in place; (2) the proportion of patients in the company model following the treat-to-clear strategy (10%) was informed by clinical opinion on PET scanner and tracer capacity in the UK; (3) results from an online survey, with responses from 17% of UK Nuclear Medicine sites, indicate that PET scanners are currently used to monitor amyloid levels in Alzheimer's disease in at least 13 UK centres,[4] (4) the NHS England submission estimated that 15% of people would have an amyloid-PET scan.[5] Based on the above, the company considered it can be assumed that monitoring will be available in some capacity in the UK, although it is acknowledged that the exact level is uncertain.

In the company's revised base case following draft guidance they kept the original assumption that 10% of patients will follow the treat-to-clear strategy, being monitored for amyloid clearance at 6 months or 12 months, with all patients stopping treatment by 18 months. The company conducted scenario analyses using different proportions of patients following the treat-to-clear strategy (company response to the draft guidance document (DGD), Table 11) and concluded that changes to this assumption have a minimal effect on the model results.

The EAG notes again that the clinical experts advising us in the original submission believed the current PET scan infrastructure in the UK was likely to be sufficient to confirm patient's eligibility to receive treatment with donanemab but that it was unlikely that patients would be monitored with PET scans to confirm amyloid clearance during treatment.

The aim of the online survey mentioned by the company was to evaluate the use of Brain SPECT and PET scans in the UK.[4] We note that 13 UK centres (32.5%) provided amyloid PET imaging, in which Alzheimer's disease was the primary indication of the scan, 17% of which performed these scans for research purposes only.[4] Only 15% of these centres (around 2 centres) performs more than 10 scans per month.[4] The EAG notes that the paper did not specify that the 13 UK centres performing amyloid PET imaging were doing it for monitoring purposes, although the company's statement implies this.

The EAG acknowledges that there is the capability to perform PET scanning and that some centres are doing it at a certain level already. However, it is unclear whether there is the capacity to do a lot more since PET scanning will be needed to confirm eligibility to receive treatment if donanemab is recommended. This will likely impact on the capacity to monitor for amyloid clearance. It is uncertain what effect diagnosing Alzheimer's disease will have on the capacity for monitoring for amyloid clearance during treatment.

As stated in the DGD[5] and argued by the company, the NHS England submission estimated that 15% of patients would have an amyloid-PET scan and most people would continue donanemab treatment for 18 months. NHS England submitted a new response following the DGD clarifying their view on the UK capacity for amyloid monitoring at 6 and 12 months. They believe the reality of treatment duration in the UK must fall between one of two scenarios: (A) 15% of patients at 6 months and 17% at 12 months are monitored for amyloid clearance; and (B) no patients are monitored for amyloid clearance during treatment. But we note that NHS England does not hold any independent information on which to base donanemab treatment duration, instead they relied on data provided by Eli Lilly and/or information available within the product's license.

The EAG considers that the company's assumption of 10% of patients following a treat-to-clear strategy falls somewhere between the two NHS England scenarios. Therefore, we use this proportion in the EAG revised base case (see EAG preferred assumptions in section 4.1).

2.4 Comment 4: Treatment waning assumptions within the model

In their original submission, the company assumed that (a) the full treatment effect was applied while patients receive treatment with donanemab; (b) after stopping treatment with donanemab (except if this happens due to patients progressing to the severe health state), the full treatment effect was retained for 3.5 years, until patients have reaccumulated amyloid up to a 'positive' level of >24.1 centiloids (CL); (c) and then the treatment effect was assumed to wane gradually over five years until disease progression rates matched those of patients who have not received treatment. In contrast, the EAG assumptions were: (a) full treatment effect while patients receive treatment with donanemab; (b) full treatment effect retained for one year after stopping treatment; (c) followed by the waning of treatment effect over 2.5 years. The committee requested a justification from the company for the proposed link between the amyloid-reducing effects of donanemab and clinically relevant changes in cognition and function in Alzheimer's disease that informed the long-term treatment assumptions. Also, the committee preferred the EAG's base case long-term treatment-effect assumptions (full treatment effect and waning), although it asked for other scenarios to be explored by the company.

The company provided additional details on the link between the amyloid-reducing effects of donanemab and clinically relevant changes in cognition and function in Alzheimer's disease. Figures 3 and 4 of the company response to the DGD show the CDR-SB and iADRS results from TRAILBLAZER-ALZ 2 trial, supporting the dose dependent increase of amyloid plaque levels and functional decline.[1] Other studies also indicated that the degree of amyloid burden was the strongest predictor of functional decline,[6; 7] with one of them showing that decline in memory performance in cognitively normal patients occurred largely when Aβ levels exceeded 68 CL.[7] Another study demonstrated that a significant change in tau PET standardised uptake value ratio (SUVR) only occurred in cognitively normal participants with an amyloid level >68 CL, and the increase in tau PET (rather than Aβ elevation) is temporarily linked to overt cognitive impairment.[8]

The company did not agree with the committee's and EAG preferred long-term treatment effect assumptions. They argued that:

- van der Kall et al. (2021) reported that patients with an amyloid plaque level of 26–50 CL at baseline showed little clinical progression until 4.5 years of follow-up (Figure 2).[9]
- Quenon et al. (2024) reported that an intermediate amyloid burden defined as 12–50 CL was not associated with an increased risk of clinical progression after 3.4 years.[10]
- Sperling et al (2024) reported that patients with an amyloid plaque level <46.1 CL showed minimal functional decline, and patients with amyloid plaque levels between 46.1–77.2 CL at baseline demonstrated decline at later timepoints over 4.5 years compared with patients with amyloid plaque levels >77.2 CL.[6]

Based on the updated clinical data following the confirmed marketing authorisation (see section 2.1 above), the company recalculated the time taken for a return to an amyloid plaque level >24.1 CL. So, in the revised company's base case following draft guidance, a full treatment effect was retained for four years after stopping treatment and then a gradual wane was applied over nine years (see Table 3 below). Nine years is the time after which amyloid levels will reach a value of 50 CL at a re-accumulation rate of 2.8 CL per year assuming that a residual treatment effect is observed at an amyloid plaque level >24.1 CL.

We note that the company kept their original assumptions for patients stopping treatment due to adverse events or due to progressing to the moderate health state – waning for 2.5 years after 1 year of full treatment effect for the first group and no treatment effect once patients progress for the second group –, which are similar to the assumptions in the EAG original base case.

The company conducted scenario analyses assuming different long-term gradual waning durations (3, 5, 7 and 11 years), keeping a full treatment effect for 5.5 years as in the revised company's base case (company response to the DGD, Table 13). The ICERs ranged between £11,556 and £15,955 per QALY.

The EAG considers that the link between amyloid clearance and short-term clinical benefit has been demonstrated in the TRAILBLAZER-ALZ and other amyloid targeting therapy trials. We also acknowledge the company's new evidence supporting this link. However, we consider that the long-term link is very uncertain and the precise mechanism through which amyloid and cognitive decline are related is still unclear. We note that the clinical experts advising the EAG in the original company submission were also unclear about the link between amyloid clearance and clinical benefit.

The company estimated that the time taken for a return to amyloid positivity after treatment discontinuation was four years, based on the PET-imaging amyloid plaque level at week 76

in the TRAILBLAZER-ALZ 2 trial (based on the updated clinical data following marketing authorisation) and assuming a re-accumulation rate of 2.8 CL per year. We reiterate our clinical experts' comments to the original company submission that they were very uncertain about assuming that full treatment effect was retained for 3.5 years after stopping treatment as there was no long-term data available to support it, although they acknowledged the results of the treatment-exposure model simulations conducted by the company, which suggested that a re-accumulation rate of 2.8 CL per year was a reasonable assumption. We also note that this median re-accumulation rate was predicted by simulations in a treatment-exposure model informed by data from four donanemab clinical trials (AACD, TRAILBLAZER-ALZ 2, TRAILBLAZER-ALZ and TRAILBLAZER-EXT). Therefore, this is not informed by long-term evidence, and it is uncertain whether the same linear rate of re-accumulation would be observed in the long-term.

Therefore, we disagree with the company's revised assumptions following draft guidance and summarised in Table 3 below and keep our original assumption: patients treated with donanemab will retain the full treatment effect for one year after stopping treatment, based on trial evidence showed in Shcherbinin et al.[11] and CS Figure 18. This assumption should be applied to patients who are treated for a fixed period of 18 months, and to those who stop treatment after reaching amyloid clearance or due to adverse events. However, as the subgroups of patients who are treated for a fixed period of 18 months and who stop at six or 12 months due to amyloid clearance are not subsequently modelled separately, this means that all patients retain the full treatment effect until the end of cycle four and therefore patients who reach amyloid clearance at six or 12 months are assumed to retain the full treatment effect for a period of 1.5 or two years after stopping treatment (rather than one year). For patients progressing to the moderate health state, no treatment effect was applied once patients progress (as in the company's original and revised base case).

The company presented some evidence that clinical progression and functional decline only occurred after 4-5 years of follow-up for patients with amyloid levels between 26-50 CL (company response to the DGD, Figure 2[9]).[6; 9; 10] Therefore, in the EAG revised base case, we apply a waning period of five years until the probability of disease progression is the same as for patients on BSC (see Table 3). We note however the uncertainty around this assumption as the cohort of patients in these studies (van der Kall et al.,[9] Quenon et al.[10] and Sperling et al.[6]) is different from the cohort of patients in the economic model - cognitively normal participants or with an MMSE 25-30 at baseline versus patients with MCI or mild Alzheimer's disease dementia at baseline that reached amyloid positivity after cleared their amyloid due to treatment with donanemab. It is unclear whether the rate of

functional decline and clinical progression is similar before and after having your amyloid cleared.

The EAG notes that the company only conducted scenario analyses around the gradual waning of treatment effect and not around the full treatment effect period. Therefore, we added a couple of scenario analyses to explore this assumption – 2 and 4 years of full treatment effect after stopping treatment (see section 4).

Table 3 shows the company's and EAG original and revised assumptions around the treatment effect of donanemab after stopping treatment due to ending the fixed treatment period of 18 months or due to amyloid clearance at six or 12 months.

Table 3 Company's and EAG original and revised assumptions around the treatment effect of donanemab

	Original company base case	**EAG base case**	**Revised company base case following draft guidance**	**Revised EAG base case**
Within trial	Full effect maintained for 18 months			
Post-trial: medium term	Full effect maintained for 3.5 years based on the average time to return to an amyloid plaque level of 24.1 CL	Full effect maintained for 1 year based on evidence from patients who cleared amyloid at 6 months in TRAILBLAZER-ALZ 2 trial	Full effect maintained for 4 years based on the average time to return to an amyloid plaque level of 24.1 CL	Full effect maintained for 1 year based on evidence from patients who cleared amyloid at 6 months in TRAILBLAZER-ALZ 2 trial
Post-trial: long-term	Gradual waning over 5 years, assuming residual treatment effect at an amyloid	Gradual waning over 2.5 years, aligning with the average time to return to an	Gradual waning over 9 years, assuming residual treatment effect at an amyloid plaque level	Gradual waning over 5 years, aligning with the approximate time for patients with amyloid levels of 26-50 CL start

	plaque level >24.1 CL	amyloid plaque level of 24.1 CL	>24.1 CL, with no treatment effect remaining at an amyloid plaque level of ~50 CL	showing a significant clinical progression and functional decline.[6; 9; 10]

2.5 Comment 5: Source of mortality risk data

In their original submission, the company applied a single hazard ratio for mortality of 2.55 (relative to the general population) for patients with mild, moderate and severe Alzheimer's disease dementia. The EAG considered it was more appropriate to use mortality hazard ratios that increase with increasing disease severity, and we used data from Crowell et al.[12] in our original base case. In response to clarification question B17b, the company included an option in the model 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. The committee preferred the EAG's source for the hazard ratios for mortality, which included an assumption that the risk of death increases as Alzheimer's disease becomes more severe.

In their response to the DGD, the company acknowledged that mortality risk may differ between the stages of Alzheimer's disease dementia and as such, have revised their base case to include differential mortality risks for the different health states. However, the company used their own NACC mortality analysis to inform their revised base case since they consider the Crowell study[12] has several limitations and provides less relevant data than their own NACC analysis. They provide the following arguments:

- **Population**: the Crowell et al analysis did not limit to biomarker-confirmed AD patients, and it is therefore likely that the sample included patients with other forms of dementia. Other forms of dementia have been shown to have a higher mortality risk compared to AD (as demonstrated in Figures 5 and 6 of the company's response to the DGD), which means that the EAG analysis would overestimate the mortality risk associated with AD.
- **Reference group**: Crowell et al. use the subset of cognitively normal individuals as the reference cohort, whereas the company NACC analysis considers individuals with MCI due to AD as the reference cohort. This difference in reference cohort means that the Crowell et al. hazard ratios are likely to be inflated. Also, Crowell et al generated a hazard ratio for MCI due to AD of 0.73 (0.55–0.96) which suggests a

survival benefit for patients with MCI due to AD versus the general population. This calls into question the validity of the dataset.

- **Methodology**: Crowell et al. censored patients upon progression to the next disease stage and the hazard ratios obtained from this model represent the relative risk of death for each disease stage, considering only the survival time within each stage. In contrast, the company NACC analysis did not censor patients upon progression to a new stage but continued to follow them until death or administrative censoring, and therefore considers the cumulative effect of time spent across different stages of the disease spectrum.

Also, the company acknowledges that conceptually the lower mortality rate for patients with moderate AD dementia compared to mild AD dementia may lack face validity. But states that these values are not statistically different and there is likely no true difference between mild and moderate. This aligns with the opinion of the clinical experts advising the company who expected that there would only be a notable increase in risk of death in those within the severe dementia category.

The EAG notes that biomarker data were only available for a small group of participants (47 participants with MCI due to AD) in the Crowell et al. study[12] and therefore was not used to confirm Alzheimer's disease aetiology. The authors consider that this may have caused them to misclassify both Alzheimer's disease and non-Alzheimer's disease participants, especially in MCI due to AD since the symptoms are normally less recognisable. In a previous NACC study, investigators reported that 83.3% of participants with clinically probable Alzheimer's disease actually met neuropathologic criteria for Alzheimer's disease.[13] The eligibility criteria to participate in the Crowell study are shown in the paper's Additional file 1.

Regarding the cohort used as the reference group (cognitively normal participants or MCI due to AD patients) and the impact it can cause in the analyses' results, we summarise some of the Crowell's study[12] conclusions below:

- The Crowell et al. study eligibility criteria were more restrictive for Alzheimer's disease cohorts compared with cognitively normal participants, as participants with a record of non-Alzheimer's aetiologic diagnosis potentially causing cognitive impairment before or at index were excluded. The authors considered that this may have resulted in an underestimation of the relative mortality in MCI due to AD compared with cognitively normal participants. The EAG considers that this might

explain the hazard ratio of 0.73 (0.55–0.96), suggesting a counter-intuitive survival benefit for patients with MCI due to AD compared to cognitively normal participants.

- The cognitively normal participants in the Crowell et al. study have a longer average life expectancy than the general US population: cognitively normal participants aged 85 years and above had a median survival of 9.4 years (women) and 7.2 years (men), while the 85-year median expected survival in the US is 7.1 years for women and 6.0 years for men. This may have led to an underestimation of the mortality in cognitively normal participants and therefore to an overestimation of the relative risk of death in Alzheimer's disease.
- Another limitation of the Crowell's study is the possible risk of bias due to informative censoring which most likely should have caused the authors to underestimate the relative risk of death in Alzheimer's disease, in the case of relatively healthy participants in each cohort had a higher likelihood of continuing in the study and not being lost to follow-up.
- The main conclusion is that the limitations presented and discussed in the Crowell's paper are likely to cancel each other out to some degree, although the uncertainty of whether the Crowell's analyses over- or underestimate the true increase in the risk of death in Alzheimer's disease still remains.

Based on the above, the EAG considers it is unclear whether the Crowell's results are overestimated. But we note that overall, the authors concluded that the risk of death for patients with MCI due to AD and cognitively normal participants was not significantly different after controlling for confounding factors.

The EAG also notes that the full methods of the company's NACC analysis are not available to us and therefore a similar inspection of the company's analysis as done for the Crowell et al. study is not possible. We consider that a better understanding of the strengths and limitations of the company's NACC analysis is necessary to provide sufficient grounds for decision-making.

Below, Table 4 (a reproduction of Table 33 of the EAG report) shows the hazard ratios of mortality used (a) in the company's original base case, (b) in the company's revised base case following draft guidance (company's NACC analysis), (c) in the cost-effectiveness studies by Ross et al.[14] and Lin et al.,[15] (d) in the study by Crowell et al.[12] for the age of 65 years, and (e) in the EAG base case (Crowell et al. for the age of 80 years, based on the US NACC UDS). According to the hazard ratios shown in Table 4, the EAG notes that the company's hazard ratios (both for their original and revised base cases) are the lowest. We also note that the EAG base case hazard ratios (Crowell et al. for 80 years) are between the

Ross and Lin cost-effectiveness studies inputs for mortality. Therefore, we still consider that the values from the Crowell study for patients at age 80 years may provide a good approximation to the mortality of the model population. Therefore, we keep the hazard ratios from Crowell et al. in our EAG revised base case (section 4.1) and explored the impact of this assumption in scenario analyses, by using alternative hazard ratios from the Ross and Lin studies, and the company's NACC analysis.

Table 4 Hazard ratio of mortality compared to general population.

Health state	Company's original base case (ONS)	Company's revised base case following DG (NACC data)	Ross et al. [14]	Lin et al.[15]	Crowell et al. (NACC data) –age 65 years[12]	EAG base case Crowell et al. (NACC data) – age 80 years[12]
MCI due to AD	1	1	1.61	1.82	1	1
Mild AD dementia	2.55	1.79	2.23	2.92	6.7	2.4
Moderate AD dementia	2.55	1.75	3.10	3.85	14.8	3.1
Severe AD dementia	2.55	3.41	4.98	9.52	30.1	6.6

Source: Reproduced from CS Table 29, Ross et al. 2022,[14] Lin et al. 2022,[15] and Crowell et al. 2023.[12]
AD, Alzheimer's disease; DG, draft guidance; MCI, mild cognitive impairment; NACC, National Alzheimer's Coordinating Centre.

2.6 Comment 6: Use of proxy EQ-5D utility values

In their original submission, the company applied patient's health state utility values assessed by caregivers using EQ-5D data obtained from the meta-analysis of Landeiro et al. 2020.[16] The pooled estimates from Landeiro et al. combined EQ-5D scores using different countries' value sets, which are 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. In contrast, we used proxy-rated patient utilities from the GERAS study measured by EQ-5D scores using a UK value set in our original base case.[17] The committee requested further considerations from the company of proxy utility values and adaptation by people living with Alzheimer's disease. Also, the committee preferred the EAG's base case for patients' utilities, but it also asked for further justification of the company's (and EAG's) approach.

The company provided additional details about the use of carer-proxy utilities in their response to the DGD. First, they noted the challenge of obtaining plausible HRQoL data

directly from patients at more severe disease states due to their cognitive decline. A study by Jönsson et al[18] also highlighted the difficulty for patients with mild to moderate cognitive impairment in completing the EQ-5D questionnaire, due to problems understanding the questions. In addition, the company considered that utilising the carer-proxy EQ-5D data for all disease states ensures that there is no uncertainty introduced by the mixing of patient and carer responses. Lastly, the company noted that in a previous NICE appraisal for the treatment of Alzheimer's disease (TA217), proxy utilities were accepted by the committee as appropriate.[19]

The EAG's assumption that the utility value for people in the MCI due to AD health state was the same as the general population was aligned with the company's base case and we have no further comments on this issue. However, the company disagrees that the GERAS study utilities[17] are the most appropriate for the current model and used data from Landeiro et al.[16] in their revised company base case following draft guidance. They argue that data from the GERAS study are conservative as this study was conducted in the community setting and therefore it is not likely to have captured the more severe cases of Alzheimer's disease. The GERAS study MMSE definition of moderately severe/severe Alzheimer's disease was MMSE < 15, where moderate Alzheimer's disease is generally defined by an MMSE score between 10-20.[17] The company concluded that this suggests that the utility values for patients with severe Alzheimer's disease dementia are likely overestimated.

As explained in the original EAG report, we agree with the company's choice of using the caregiver assessment as a proxy to patient utilities. But we acknowledge that proxy utility data are not ideal and need to be interpreted with caution, particularly in patients in the earlier stages of the disease who might be able to meaningfully assess their own HRQoL. Again, we note that changing the patient utility values for the mild health state has a minimal impact in the model results.

The GERAS study has several limitations that can influence the external validity of the study, one of which is the fact that the utilities may not be representative of patients with more severe Alzheimer's disease living in the community since only 40% of the moderately severe/severe group had a MMSE score < 10.[17]

Regarding the use of the Landeiro study[16] to inform patient utilities in the revised company's base case following draft guidance, we reiterate that it does not follow the NICE Reference case by combining EQ-5D scores using different countries' value sets.[20] Also, we note that it is not clear whether utilities based on value sets for other countries are generalisable to the UK and whether using other value sets might over- or under-estimate the utilities.

In addition, we note that the GERAS study[17] contributed with the biggest number of patients to the Landeiro pooled utilities for mild, moderate and severe dementia health states.[16] This means that the researchers in Landeiro et al. considered the GERAS study to be useful to contribute data for the severe health state, even though this study might not be representing patients with more severe stages of Alzheimer's disease dementia (as discussed above). Similarly, Landeiro et al.[16] may include other studies not fully representing all the stages of Alzheimer's disease dementia and therefore the pooled utilities can be an over- or underestimation of the true quality of life of patients. A thorough analysis of the studies included in the meta-analysis of Landeiro et al. would be needed to check for this.

As the company did not present any new evidence on this point and as the committee preferred the EAG's approach, we maintain our position and use utility values from the GERAS study[17] in our revised base case (see section 4.1 below).

2.7 Comment 7: The approach to deriving carer utilities

In their original submission, the company applied caregiver utilities derived from two vignette studies conducted by the company using the time trade-off approach measured by general population participants.[21] As using time-trade-off utilities reported by general population participants did not meet the criteria for the NICE Reference Case, the EAG used EQ-5D scores directly assessed by caregivers in our base case, reported in the GERAS study.[22] We applied the same utilities regardless of the type of caregiver (spouse or child) and the setting where the patient lives (community or residential care). The committee requested further information from the company on the vignette studies and further justification for using this approach for carer utilities. Also, the committee preferred the EAG's base case for carer utilities, but it also asked for further justification of the company (and EAG) approach.

The company provided additional details on the use of the vignette studies. First, the company argues that EQ-5D is not an appropriate measure to estimate utilities associated with being a carer for patients with MCI due to AD or mild AD dementia. The company's reasons are outlined below:

- The EQ-5D was designed to quantify an individual's overall health status and as such, the five dimensions have limited relevance to caregiver utility.
- Caregivers contacted by the company as part of the production of the vignette studies reported that the most common areas of impact for them were (1) uncertainty regarding whether their loved one can understand or remember things, (2) work-related impact, (3) the loss of time to themselves, (4) irritation/frustration, (5) having

to learn how to perform tasks for which they were previously not responsible, and (6) having to handle all the driving. Based on these, the company considered that EQ-5D was unable to capture the most important aspects of caregiver impact, demonstrating the lack of content validity in this circumstance.

- Published literature supports that EQ-5D is not an adequate tool for assessing the utility of caregivers of Alzheimer's disease patients: Reed et al.[23] suggests that EQ-5D is not particularly effective at capturing the true impact on caregivers of caring for patients with Alzheimer's disease dementia; Sokolova et al.[24] found a ceiling effect and failed to differentiate between caregivers of patients with moderate and severe Alzheimer's disease.
- The Spillovers in Health Economic Evaluation and Research (SHEER) task force highlighted the absence of suitable tools for evaluating caregiver spillover effects in health economic analyses. They emphasise the need for developing novel preference-based measures specifically designed to capture these health spillovers due to the lack of empirical evidence supporting any existing instruments.[25]
- A publication from the EuroQol Group recognised that the EQ-5D falls short in accurately reflecting the impact of a patient's health on their carers.

Second, the company considers that other generic and condition-specific instruments are likely to have the same limitations as EQ-5D and are unlikely to be sensitive to the impact of caring for a close relative with MCI or dementia associated with Alzheimer's disease.

Lastly, due to the reasons above, the company derived carer utilities from two vignette studies conducted by them based on a time trade-off approach, as it is recommended by NICE for situations in which use of EQ-5D is not appropriate.

Therefore, the company maintains that the vignette-based studies are a more appropriate method to estimate carer utilities than the EAG's base case approach using EQ-5D data from the GERAS study. As already stated in Comment 6 of their response to the DGD, they also reiterated that the data from the GERAS study can be overly conservative as this study was conducted in the community setting and therefore has not captured the more severe cases of Alzheimer's disease. In addition, the company consider that the EQ-5D data from the GERAS study lacks face validity as (1) there are limited differences in utility values for caregivers of patients across the three stages of Alzheimer's disease dementia (range of 0.04), (2) the EAG adjusted the data in the model because EQ-5D estimates for caregivers of mild AD dementia patients in the GERAS study were higher than the general population, and (3) the median value for all health states for the EQ-5D caregiver utility is 0.89 which is above the general population value.

Regarding the use of the vignette studies, the company considered that the utility data used in their original base case is more appropriate than the utility data suggested in an EAG scenario analysis (see EAG report Table 37) and used the original data in their revised company base case following draft guidance. They believe that utilities should be split both by type of caregiver (spouse or child) and by residential status (community or residential care setting). In the EAG's scenario, the HRQoL of a child caregiver for a patient living within the community is assumed to be the same as for a patient living within residential care. In the company's opinion, this underestimates key aspects of caring for someone in the community who does not have constant care.

The company conducted a scenario analysis to include utility values for carers living with patients (previously spouse carers in the community) and carers not living with patients (previously child carers in the community and all carers in residential settings), as per the EAG's scenario analysis (company response to the DGD, Table 16). This change had a minimal effect on the model results.

The company also commented on the number of caregivers per patient used in the EAG's base case and preferred by the committee: one caregiver per patient. They acknowledge the lack of published evidence on the utilities for secondary carers of patients with Alzheimer's disease and that the disutility impact may differ between primary and secondary carers. However, they consider that one caregiver per patient underestimates the impact of Alzheimer's disease and treatment with donanemab on caregiver quality of life, and that it is reasonable to expect that the burden of secondary caregivers is greater than zero and therefore the EAG's approach is conservative. The company modelled 1.8 caregivers per patient in their original base case and also in their revised base case following draft guidance. This was based on data from the GERAS study.[26] They tested this assumption in scenario analyses and applied different values for the number of caregivers (company response to the DGD, Table 17) and concluded that reducing the number of caregivers per patient increases the ICER to £14,073 when 1.2 caregivers per patient are modelled.

The EAG acknowledges that EQ-5D might not be the most suitable instrument to estimate utilities associated with being a carer for patients with Alzheimer's disease and the need for developing new measures specifically designed to capture the impact of the disease on the health-related quality of life of caregivers.

However, we note that most of the aspects that the caregivers of patients with Alzheimer's' disease 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.

Moreover, the vignette studies did not meet the NICE Reference Case[20] as they used the time trade-off approach and utilities were reported by general population participants, rather than caregivers for patients with Alzheimer's disease. The vignette studies are also associated with several limitations, which are outlined below:

- Limitations related to the health state development
    - The vignette descriptions are unlikely to include all aspects of the carer experience within a health state, which might affect the validity of the derived utilities.[21]
    - The health state descriptions might have been misinterpreted and participants could struggle to distinguish between vignettes.
    - Limited number of primary sources that may have led to a depiction of caregiving that is not fully representative.[21]
- In the second vignette study, the proportion of respondents older than 61 years was lower than the UK average while the proportion with higher education was higher than the UK average.[21]
- In this study, respondents were required to imagine themselves as a care partner of a patient and not to imagine their own health states, which adds uncertainty to the generalisability of these utility values to the utilities experienced by carers in clinical practice.[21]
- The utilities estimated by the vignette studies seem to lack face validity and to be unrealistic as some of them (mainly in the community setting) are similar or even lower than the patient utilities.

The limitations of the vignette studies mentioned above as well as the fact that it does not meet the NICE Reference Case, makes us reluctant to use the company's utility estimates. Also, NICE guidance states that the EQ-5D is the preferred instrument to measure health-related quality of life in adults.[20]

Therefore, as in our original base case, we consider the GERAS study utilities[22] to be informative for the current economic model in the absence of better utility sources of data. Again, we did not stratify the utilities of caregivers by type of caregiver and community or residential care setting as it will require several assumptions to be made, which would add uncertainty to the results. But we note that the GERAS study included both child and spouse caregivers and that the study was conducted in the community setting, where we can expect

the burden in caregivers to be higher. We explore this assumption in scenario analyses as we note the uncertainty of assuming a similar utility for patients living with the patient or living separately from the patient with Alzheimer's disease (see section 4.2). See the EAG base case and scenarios inputs in Table 5 below.

EAG scenario 1 is the EAG base case with alternative values for the spouse caregivers in the community setting and EAG scenario 2 is the EAG base case with alternative values for the spouse and child caregivers in the community setting. Spouse and child caregivers' utilities in the community setting were taken from the EAG scenario reported in Table 37 of the EAG report and are explained in the paragraph above Table 37 of the EAG report.

Table 5 Caregiver utilities

	EAG base case (GERAS adjusted)[a]	**EAG scenario 1 (based on the company's vignette studies [b] + GERAS adjusted for child and residential)**	**EAG scenario 2 (based on the company's vignette studies [c] + GERAS adjusted for residential)**
Spouse caregiver in the community setting			
MCI	0.81	0.82	0.82
Mild	0.80	0.79	0.79
Moderate	0.79	0.65	0.65
Severe	0.76	0.49	0.49
Child caregiver in the community setting			
MCI	0.81	0.81	0.84
Mild	0.80	0.80	0.74
Moderate	0.79	0.79	0.71
Severe	0.76	0.76	0.64
Child and spouse caregiver in the residential care setting			
MCI	0.81	0.81	0.81
Mild	0.80	0.80	0.80
Moderate	0.79	0.79	0.79
Severe	0.76	0.76	0.76

Source: Reed et al. 2017;[22] Eli Lilly data on file 2023; Belger et al. 2022.[21]
EAG, Evidence Assessment Group.
[a] MCI and mild health states were assumed to be similar to general population with the same age (67.8 years) and gender distribution (36.4% males) as the caregiver population in the economic model for these two health states; utility for MCI was assumed to be the general population utility for age 67

years and for mild was assumed to be for age 68 years. Moderate and severe utilities are the GERAS study utilities adjusted to be lower than the general population utilities (moderate: 0.85*0.80/0.86=0.79; severe: 0.82*0.80/0.86=0.76).
[b] This scenario differs from the EAG base case as it considers the utilities from the vignette studies for the spouse caregiver in the community setting: for MCI, the utility comes from the primary vignette study for the spouse caregiver health state, while for mild, moderate and severe, the utilities come from the secondary vignette study for caregivers living with patients with mild, moderate and severe Alzheimer's disease.
[c] This scenario differs from the EAG scenario 1 as it also considers the utilities from the vignette studies for the child caregiver in the community setting: for MCI, the utility comes from the primary vignette study for the parent caregiver health state, while for mild, moderate and severe, the utilities come from the secondary vignette study for caregivers living separately from patients with mild, moderate and severe Alzheimer's disease.

We agree with the company that, although the quality-of-life impact on a primary and secondary caregiver is not the same, it is also reasonable to expect that the burden of secondary caregivers is greater than zero. This means that our approach of assuming that the impact on quality of life of only one caregiver per patient is taken into account in the model is likely to be conservative. However, in the same way, assuming a similar impact on quality of life for 1.8 caregivers per patient is likely to be an overestimate, as we believe that the primary caregiver would be expected to have a greater impact on their quality of life than secondary caregivers. Again, there is no published evidence to inform the utility estimates for the secondary caregivers. So, we modelled 1.2 caregivers per patient, for which the same GERAS utilities were applied for the primary and secondary caregivers, in an attempt to capture how the quality of life of 1.8 caregivers (1 primary caregiver and 0.8 secondary caregivers) is affected. This means that we are assuming that secondary caregivers have a 75% lower impact in their quality of life than the primary caregivers. We explore scenarios where we change the number of caregivers between one and 1.8 in the EAG base case (see section 4.2).

2.8 Comment 8: The anticipated infusion cost associated with treatment with donanemab

The company use an estimated infusion cost of £207.59 (NHS reference costs SB12Z) compared to an estimated infusion cost of £565 from NHS England (NHS reference costs WD02Z). The committee wished to see more explanation from the company and NHS England, including a breakdown of expected resource use that explained the estimated costs.

The company provide more detail of the administration cost, i.e., that it is associated with delivering simple parenteral chemotherapy at first attendance. This is considered appropriate by the company as it is consistent with an administration time of 30 minutes and observation of patients for 30 minutes. They also note that for the NHS England estimate, this HRG code

no longer exists and although it is a disease-specific code it is not related to drug administration and assumes that donanemab should be administered over a full day of mental health treatment by a non-specialist. They also note that NHS England proposed a different infusion cost for the STA for lecanemab of £432. The company conduct scenario analyses using different administration costs (company response to DGD, Table 18) and conclude that changes to the administration costs have a minimal effect on the model results.

NHS England have provided evidence on infusion pricing options. They considered that an appropriate alternative method for estimating the costs for modelling and appraisal purposes is to use an approach consistent with the pricing assumed within the NICE appraisal process for monoclonal antibodies (MABs) administered in the management of a confirmed COVID infection. Using this method, and subject to a coding guidance and practice change, NHS England's pricing team estimate a resulting indicative unit price, including Market Forces Factor (MFF), of £432. NHS England note that there is not currently a reference cost code for administration of donanemab but consider that the cost would be higher than the cost of administering chemotherapy as it requires more complex preparation prior to administration and carries a higher risk of adverse infusion reactions.

On the basis of NHS England advice, we use their recommended infusion cost of £432 for donanemab administration in our revised base case (see section 4.1).

2.9 Comment 9: Disaggregated results for individual health states

The committee requested results disaggregated, discounted and undiscounted results for the individual health states in the revised base case. The company supplies these in the company response to DGD, Tables 19, 20 and 21. The EAG has checked these results, and we can verify that these are correctly reported.

2.10 Comment 10: The proportion of patients starting in the MCI due to AD and mild AD dementia health states

In their original submission, the starting distribution of patients across MCI due to Alzheimer's disease and mild Alzheimer's disease dementia health states in the economic model was taken from the TRAILBLAZER-ALZ 2 trial (20.4% in MCI due to Alzheimer's disease and 79.6% in mild Alzheimer's disease dementia). We used the same distribution in our original base case.

The marketing authorisation includes a stopping rule which means patients should stop donanemab treatment once they reach the moderate Alzheimer's disease stage. The

company make the case for updating the starting distribution of patients across MCI due to Alzheimer's disease and mild Alzheimer's disease dementia health states in the economic model because of this stopping rule. The company state that this is because clinical expert opinion suggests that clinicians would be more likely to initiate treatment at an earlier stage of disease to avoid the risk of having to apply this stopping rule and to enable, where possible, patients to receive the full course of donanemab. The company also point out that the EAG assigned to the lecanemab appraisal estimated that the starting distribution of patients initiating lecanemab treatment would be 38% in MCI due to Alzheimer's disease and 62% in mild Alzheimer's disease dementia. The company also cite two real-world evidence sources[27; 28] and updated their base case in line with the most recent of these. The sources are summarised below in Table 6. We also acknowledge that if a disease-modifying treatment for MCI due to Alzheimer's disease and mild Alzheimer's disease dementia becomes available within the NHS this may lead patients to present for treatment earlier than happens currently, but the extent to which this might occur is unknown.

Our preference for the EAG base case is to maintain the alignment of the evidence source for the starting distribution of patients across MCI due to Alzheimer's disease and mild Alzheimer's disease dementia health states and the source of effectiveness data. Ideally, we would use the proportions from the combined TRAILBLAZER-ALZ 2 and TRAILBLAZER-ALZ populations that correspond to the UK eligible population as described in the donanemab marketing authorisation. Unfortunately, this is not possible because the required data for the UK eligible population are not reported. Therefore, we continue to use the proportions from the TRAILBLAZER-ALZ 2 trial in our base case and use the proportions from Kile et al.[28] in a scenario analysis.

Table 6 Summary of evidence sources for the proportion of patients starting donanemab treatment in the MCI due to Alzheimer's disease and mild Alzheimer's disease dementia health states

Source and usage	Proportion starting in health states	Number of patients	EAG comments
TRAILBLAZER-ALZ 2[3] Company and EAG base cases	20.4% in MCI 79.6% in mild AD	1736	Aligned with source of effectiveness data. Categories of MCI and mild AD based on MMSE.

Source and usage	Proportion starting in health states	Number of patients	EAG comments
EAG estimate lecanemab appraisal[29]	38% in MCI 62% in mild AD	1734	This estimate appears to be a reversal of the proportions in the Clarity AD trial, based on clinical expert opinion which suggested patients in the UK were more likely to present at the mild dementia stage than at the MCI stage. Categories of MCI and mild AD appear to be based on National Institute on Aging–Alzheimer's Association criteria.
Shields et al. real-world evidence (lecanemab)[27]	49.3% in MCI 50.7% in mild AD	71	Small number of patients. Unclear how the categories of MCI and mild AD were assigned.
Kile et al. real-world evidence (lecanemab)[28]	70% in MCI 30% in mild AD	234	Unclear how the categories of MCI and mild AD were assigned

Source: EAG table compiled from information in the company response to draft guidance
AD, Alzheimer's disease; MCI, mild cognitive impairment; MMSE, mini-mental state exam

2.11 Comment 11: Proportion of patients transitioning to residential care annually

Following the committee's preference for the EAG source for annual risk of residential care, the company revised their base case to include those. The EAG agrees and has no further comments on this issue.

2.12 Comment 12: Inclusion of informal / unpaid carer costs in the base case

The company preferred to include the cost of informal / unpaid carer costs in their revised base case analysis following draft guidance. They justify this by referencing section 4.2.4 of the NICE manual that states that 'when care by family members, friends or a partner might otherwise have 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'.[30]

We note that the committee decided that it was not appropriate for the company to include unpaid care costs in its model. It concluded that it preferred the EAG's approach to costing healthcare resource use. We therefore have excluded informal / unpaid carer costs in our revised base case, as previously assumed in our EAG report.

2.13 Comment 13: Sensitivity analysis to reduce risk of bias in TRAILBLAZER ALZ-2 trial

As stated in the NICE donanemab draft guidance document paragraph 3.8, we raised concerns that the occurrence of ARIA events had the potential to enable participants and their carers to predict that they were in receipt of donanemab which might affect their CDR-SB responses. The committee agreed that this risk of bias should be explored further for the CDR-SB and the iADRS outcomes based on meta-analysis of TRAILBLAZER-ALZ 2 and TRAILBLAZER-ALZ. The company have conducted sensitivity analysis, and the results are provided in Table 24 of the company's response to draft guidance for the pooled UK eligible population from TRAILBLAZER-ALZ 2 and TRAILBLAZER-ALZ, with additional results for the UK eligible population in TRAILBLAZER-ALZ 2 in Table 5. Although not explicitly stated, we believe that the results have been obtained from the company's Cox proportional hazards model. For the pooled UK eligible population, censoring patients at their first occurrence of ARIA/IRR [redacted].

Overall, we are reassured that if the occurrence of ARIA events did cause participants or their carers to predict they were in receipt of donanemab this did not have a substantial impact on either the CDR-SB or iADRS outcomes. The donanemab SmPC advises that when dosing is suspended for symptomatic or radiographically moderate of severe ARIA-E or ARIA-H events, it may be resumed if MRI demonstrates the events have resolved (ARIA-E) or stabilised (ARIA-H), guided by clinical judgment. Therefore, as stated in section 2.2.2, our preference is to use the hazard ratio from the meta-analysis of TRAILBLAZER-ALZ 2 and TRAILBLAZER-ALZ (HR= [redacted]) in the economic model (i.e. without censoring patients at their first occurrence of ARIA/IRR).

2.14 Comment 14: Factual inaccuracies noted in the Draft Guidance Document

The company note a factual inaccuracy in the draft guidance document. The EAG have no further comments on this issue.

2.15 Comment 15: Updates to managed access proposal

The company comment that they are working on updating the original managed access proposal. The EAG have no further comments on this issue.

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 ICER result in Company response Table 4. The cumulative effect of the changes implemented by the company, results in an ICER of £12,091 per QALY (Table 7).

Table 7 Company revised model base case analysis with PAS

Treatment	Total costs	Total QALYs	Incr. costs	Incr. QALYs	ICER (£/QALY)
Donanemab	[redacted]	[redacted]			
BSC	[redacted]	[redacted]	[redacted]	[redacted]	£12,091

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

The EAG reviewed the company's new model, including the implementation of costs and benefits for patients, and agree that the changes listed have been implemented appropriately. We also note that several other changes have been made to the company's model that are not documented in the company response. All changes reported and identified by the EAG are shown below in Table 8. With these changes, the EAG is able to replicate the changes made between the company's previous model (seen at Committee meeting 1) and their current revised base case.

Table 8 Changes from the company's original base case

	Original parameters	Revised parameters
HR for donanemab vs BSC (comment 2)	[redacted]	[redacted]
Waning assumptions (comment 4)	Apply waning from 10 cycles, for 10 cycles.	Apply waning from 11 cycles, for 18 cycles.
A differential mortality risk between stages of AD was applied, using the company National Alzheimer's Coordinating Centre (NACC) analysis as the source of mortality data (Comment 5)	HR: 1,2.55,2.55,2.55 for MCI, mild AD, moderate AD and severe AD.	HR: 1, 1.79, 1.75, 3.41 for MCI, mild AD, moderate AD and severe AD.

The proportion of patients starting the model in the MCI due to AD and mild AD dementia health states was updated (Comment 10)	MCI 20.4%, mild AD 79.6%	MCI 70%, mild AD 30%
A revised source informing the risk of transitioning to residential care per cycle, in line with EAG base case (Comment 11)	Spackman et al.[31]	GERAS 2019[26]
Neurologist outpatient visit included in the cost of APOE-4 testing, in line with EAG base case	Cost APOE-4 test £43.81.	Cost APOE-4 test £265.72
Inclusion of one neurologist outpatient visit per cycle as a follow-up visit to monitor disease progression, in line with EAG base case	0 OP visit per cycle	1 OP visit per cycle
No terminal care costs are included, in line with committee preference at ACM1 and EAG base case	Terminal care cost £7274.	Terminal care cost £0
PAS discount for donanemab.	Original [redacted] per vial)	revised [redacted] per vial)
Treatment related mortality for the first cycle for donanemab	0.35%	0.47%
Age MCI, Mild AD years	72.81	73.32
Proportion male, MCI, Mild AD %	50.4%	49.275%
Treatment stopped after progression to health state	Severe AD	Moderate AD
Proportion of patients stopping due to amyloid clearance	6 months: 29.7%; 12 months 36.42%	6 months: 33%, 12 months: 35.8%
Discontinuation after 6 months, excluding progression	13.1%	12.4%
Trial reported incidence of adverse events	36.8%	32.9%
Percentage of events that are symptomatic	25.37%	27.27%
Infusion related reactions	3.75%	3.1%
Hypersensitivity	0.82%	1.09%
Anaphylactic reaction	0.35%	47%
Severity modifier	1.2	1.0
Coding in cell model sheet Engine!ED54 for administration costs in first cycle.	-	Part of coding removed in revised version.

The company presents the results of their probabilistic sensitivity analysis (PSA) in Company response Table 3.

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:

- Use the hazard ratio from the meta-analysis of TRAILBLAZER-ALZ 2 and TRAILBLAZER-ALZ 2 (HR= [redacted]) (section 2.2).
- Apply waning of treatment effect from 5 cycles (2.5 years) for 10 cycles (5 years), (section 2.4).
- Mortality risk taken from Crowell et al.[12] as in the EAG original base case (section 2.5).
- Patient utility values taken from GERAS study, as in the EAG original base case (section 2.6).
- Carer utility values taken from GERAS study, as in the EAG original base case, with 1.2 caregivers (section 2.12).
- Infusion cost associated with treatment with donanemab of £432, as advised by NHS England (section 2.8).
- 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 2.10).
- Exclude unpaid carer costs, as in the EAG original base case (section 2.12).

The cumulative effect of the EAG's preferred model assumptions is shown in Table 9. The EAG's base case is £135,284 per QALY.

Table 9 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]			£12,091
		BSC	£[redacted]	[redacted]	[redacted]	[redacted]	
1	Use hazard ratios from the meta-analysis (HR= [redacted])	Donanemab	[redacted]	[redacted]			£14,618
		BSC	[redacted]	[redacted]	[redacted]	[redacted]	
2	Apply waning of treatment effect from 5 cycles for 10 cycles	Donanemab	[redacted]	[redacted]			£30,836
		BSC	[redacted]	[redacted]	[redacted]	[redacted]	
3	Mortality risk for AD from Crowell et al.	Donanemab	[redacted]	[redacted]			£42,522
		BSC	[redacted]	[redacted]	[redacted]	[redacted]	
		Donanemab	[redacted]	[redacted]			£47,879

Parameter		Treatment	Total costs	Total QALYs	Incr. costs	Incr. QALYs	ICER (£/QALY)
4	Patient utility values taken from GERAS study	BSC	[redacted]	[redacted]	[redacted]	[redacted]	
5	Carer utility values taken from GERAS study with 1.2 caregivers	Donanemab	[redacted]	[redacted]			£76,617
		BSC	[redacted]	[redacted]	[redacted]	[redacted]	
6	Infusion cost for donanemab of £432	Donanemab	[redacted]	[redacted]			£89,144
		BSC	[redacted]	[redacted]	[redacted]	[redacted]	
7	Patients starting in health states: MCI 20.4%, Mild AD 79.6%	Donanemab	[redacted]	[redacted]			£125,961
		BSC	[redacted]	[redacted]	[redacted]	[redacted]	
8	Exclude unpaid carer costs	Donanemab	[redacted]	[redacted]			£135,284
		BSC	[redacted]	[redacted]	[redacted]	[redacted]	
9	EAG revised base case	Donanemab	[redacted]	[redacted]			£135,284
		BSC	[redacted]	[redacted]	[redacted]	[redacted]	

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 10). The scenarios that have the greatest impact on the model results are changes to the caregiver utility (scenario 12) and changes to the assumption of treatment waning (scenario 3).

Table 10 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]			£135,284
		BSC	[redacted]	[redacted]	[redacted]	[redacted]	
1	Use hazard ratios from the TRAILBLAZER-ALZ 2 (HR= [redacted])	Donanemab	[redacted]	[redacted]			£124,496
		BSC	[redacted]	[redacted]	[redacted]	[redacted]	
2	All patients treated for 18 months (0% follow TTC strategy)	Donanemab	[redacted]	[redacted]			£136,852
		BSC	[redacted]	[redacted]	[redacted]	[redacted]	
3	Apply waning of treatment effect from 11 cycles for 18 cycles	Donanemab	[redacted]	[redacted]			£92,039
		BSC	[redacted]	[redacted]	[redacted]	[redacted]	
4	Apply waning of treatment effect from 11 cycles for 10 cycles	Donanemab	[redacted]	[redacted]			£97,376
		BSC	[redacted]	[redacted]	[redacted]	[redacted]	
5	Apply waning of treatment effect from 7 cycles for 10 cycles	Donanemab	[redacted]	[redacted]			£115,975
		BSC	[redacted]	[redacted]	[redacted]	[redacted]	
6	Mortality risk for AD from NACC analysis	Donanemab	[redacted]	[redacted]			£150,893
		BSC	[redacted]	[redacted]	[redacted]	[redacted]	
		Donanemab	[redacted]	[redacted]			£150,935

Parameter		Treatment	Total costs	Total QALYs	Incr. costs	Incr. QALYs	ICER (£/QALY)
7	Mortality risk for AD from Ross et al.	BSC	[redacted]	[redacted]	[redacted]	[redacted]	
8	Mortality risk for AD from Lin et al.	Donanemab	[redacted]	[redacted]			£139,748
		BSC	[redacted]	[redacted]	[redacted]	[redacted]	
9	Patient utility values taken from Landeiro et al.	Donanemab	[redacted]	[redacted]			£102,581
		BSC	[redacted]	[redacted]	[redacted]	[redacted]	
10	Carer utility values: EAG scenario 1 (Table 5)	Donanemab	[redacted]	[redacted]			£105,586
		BSC	[redacted]	[redacted]	[redacted]	[redacted]	
11	Carer utility values: EAG scenario 2 (Table 5)	Donanemab	[redacted]	[redacted]			£104,517
		BSC	[redacted]	[redacted]	[redacted]	[redacted]	
12	Carer utility values taken from Belger et al with 1.8 caregivers	Donanemab	[redacted]	[redacted]			£79,920
		BSC	[redacted]	[redacted]	[redacted]	[redacted]	
13	1.4 caregivers	Donanemab	[redacted]	[redacted]			£134,218
		BSC	[redacted]	[redacted]	[redacted]	[redacted]	
14	1.6 caregivers	Donanemab	[redacted]	[redacted]			£133,169
		BSC	[redacted]	[redacted]	[redacted]	[redacted]	
15	Infusion cost for donanemab of £207.59	Donanemab	[redacted]	[redacted]			£120,439
		BSC	[redacted]	[redacted]	[redacted]	[redacted]	
16	Patients starting in health states: MCI 70%, Mild AD 30%	Donanemab	[redacted]	[redacted]			£102,807
		BSC	[redacted]	[redacted]	[redacted]	[redacted]	
17	Include unpaid carer costs	Donanemab	[redacted]	[redacted]			£125,961
		BSC	[redacted]	[redacted]	[redacted]	[redacted]	

ICER, incremental cost-effectiveness ratio; Incr., incremental; QALYs, quality-adjusted life years; MCI

5 EAG CONCLUSION

The company revised their base case following draft guidance, as discussed in section 2 and listed in Table 8.

The EAG disagrees with several of the assumptions in the company's model. Our preferred assumptions include:

- Use the hazard ratio from the meta-analysis of TRAILBLAZER-ALZ 2 and TRAILBLAZER-ALZ 2 (HR= [redacted]) (section 2.2).
- Apply waning of treatment effect from 5 cycles (2.5 years) for 10 cycles (5 years), (section 2.4).
- Mortality risk taken from Crowell et al.[12] as in the EAG original base case (section 2.5).
- Patient utility values taken from GERAS study, as in the EAG original base case (section 2.6).
- Carer utility values taken from GERAS study, as in the EAG original base case, with 1.2 caregivers (section 2.12).
- Infusion cost associated with treatment with donanemab of £432, as advised by NHS England (section 2.8).
- 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 2.10).
- Exclude unpaid carer costs, as in the EAG original base case (section 2.12).

Incorporating the EAG preferred assumptions, the ICER increases to £135,284 per QALY for donanemab vs best supportive care. The model results are most sensitive to changing the assumptions for how long the treatment effect lasts and to changing the caregiver utilities.

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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.

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	Evaluate clinical efficacy and safety between early start participants versus delayed start participants treated with donanemab	Up to 36 months (Additional 76-weeks beyond initial study)	[redacted]
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
Platform for 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

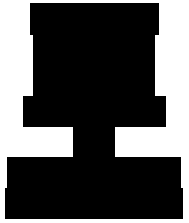
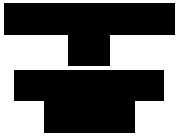
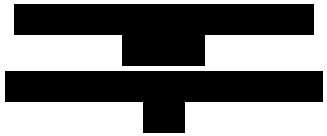
Implementation of ATTs Cost and HCRU Study	Treatment-related HCRU and costs associated with initiation of ATT's HCRU and costs of patient monitoring during ATT treatment	Retrospective UK Secure Data Environment Dataset	Q1 2027
UK Controlled Access Program	To register all patients prior to initiation 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	Evaluate clinical efficacy between early start participants versus delayed start participants treated with donanemab and safety	[redacted]	Up to 36 months (Additional 76-weeks beyond initial study)	[redacted]	Yes	Long-term clinical effectiveness Long-term safety
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 **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	18 months	Q2 2028	Yes estimated 200 patients	Confirm clinical effectiveness and safety

		level (derived from ADCS-ADL), RUD-Lite, and NPI				
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)	(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		Long-term clinical effectiveness, quality of life, institutionalization and mortality, caregiver burden
Platform for Early Alzheimer's in Real Life (PEARL)	Understand short-, medium-, and long-term real-world safety and effectiveness of treatment	Include diverse populations to understand their experiences with AD and treatment 	5-years retrospective and 5-years prospective		US data only	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). 	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	Proportion of patients with MCI due to AD or mild AD dementia	Retrospective	Q1 2025	Not applicable	Cost and resource use in health and social care

	Predictors of high cost within AD		UK Secure Data Environment Dataset			
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 intracerebral haemorrhage >1cm	Assess AE correlation with relevant risk factors Assess long-term safety events	~200 weeks, data collection terminates December 2030	[redacted]	200 UK patients	Baseline characteristics, long term safety information
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

Abbreviations: AD: Alzheimer's disease; ADAS-Cog13: 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

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): **30/12/2024**

Is Managed Access appropriate - Overall rating	Comments / Rationale
Committee judgement required	There are some ongoing trials which could generate further evidence. Data gathered via the company's proposed studies could provide some useful evidence to resolve some of the identified uncertainties - some uncertainties may not be addressed at all, and some uncertainties only partly addressed. Extensive barriers exist to both implementation and data collection in the NHS (for example, the need to add PET scanning capacity and expertise to the NHS, and the need to ask both primary and secondary care clinicians to record assessment results). No NHS-level data collection beyond baseline measurements on enrolment is proposed, therefore the most feasible way to gather further data is via the described trials rather than real-world data in clinical practice. This is advantageous as there is, therefore, no additional burden of data collection on-top of implementation, though the full implementation burden will of course be realised if this technology is offered through the IMF.

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 is sufficient.
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?

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. Whether significant or not will be determined later in the evaluation.
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	The majority of uncertainties are related to detailed technical decisions to be taken at the committee meeting with additional clinical evidence and will not be impacted or resolved by further data collection. Some uncertainties could be reduced by data collection according to the company's managed access proposal - refer to the Trial Data tab. There is currently no long-term NHS-level data collection proposed. The company does propose gathering baseline data from all patients initiated onto the technology.

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
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 extension and 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 (inc EXT and Addendum)	
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 TRAILBLAER-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.

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. PET Sub-study To determine the proportion of participants who reach amyloid clearance, 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, HRQoL

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**
Low	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 what data will become available, or what state of completeness or 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