Lecanemab
(early-stage Alzheimer's disease 1)

Addendum to Project A25-111
(dossier assessment)[1]

ADDENDUM (DOSSIER ASSESSMENT)

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List of abbreviations

Abbreviation	Meaning
AChEI	acetylcholinesterase inhibitor
ACT	appropriate comparator therapy
ADAS-COG14	Alzheimer's Disease Assessment Scale – Cognitive Subscale, 14-item version
AE	adverse event
ApoE ε4	apolipoprotein E ε4
ARIA	amyloid-related imaging abnormalities
ARIA-E	amyloid-related imaging abnormalities-oedema/effusion
ARIA-H	amyloid-related imaging abnormalities – haemorrhage
CDR	Clinical Dementia Rating
CDR-GS	Clinical Dementia Rating Global Score
CDR-SB	Clinical Dementia Rating—Sum of Boxes
CI	confidence interval
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
ITT-FAS+	patients who received at least one dose of the respective treatment and for whom a baseline value and at least one post-baseline questionnaire evaluation in the CDR were available
MCI	mild cognitive impairment
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	mixed-effects model with repeated measures
MMST	mini mental status test
PT	Preferred Term
QOL AD	Quality of Life in Alzheimer's Disease Scale
RCT	randomized controlled trial
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SMD	standardized mean difference
SOC	System Organ Class

1 Background

On 13 January 2026, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to conduct supplementary assessments for Project A25-111 (Lecanemab – Benefit assessment according to §35a Social Code Book V) [1].

In the commenting procedure and following the oral hearing, the pharmaceutical company (hereinafter referred to as "the company") presented supplementary data [2,3] which went beyond the information provided in the dossier [4]. The commission comprises the assessment of the following analyses presented by the company in the commenting procedure and following the oral hearing, taking into account the information provided in the dossier:

Analyses of the subpopulations of the CLARITY AD study whose treatment corresponds to both the marketing authorization of lecanemab and the appropriate comparator therapy (ACT) (subpopulations as defined in research question 1 and research question 2), including

- patient characteristics
- information on the course of the study (therapy/study discontinuations, missing values)
- subgroup analyses by age and sex
- stratification analyses
- safety analyses, including symptomatic and combined ARIA
- time-to-event analyses on deterioration

The responsibility for this assessment and the assessment result lies exclusively with IQWiG. The assessment is forwarded to the G-BA. The G-BA decides on the added benefit.

2 Assessment

Moreover, the following research questions are considered in the benefit assessment:

Table 1: Research questions of the benefit assessment of lecanemab

Research question	Therapeutic indication	ACT[a]
Adults with early Alzheimer's disease who are apolipoprotein E ε4 (ApoE ε4) non-carriers or heterozygotes with confirmed amyloid pathology:		
1	With a clinical diagnosis of MCI due to Alzheimer's disease	Watchful waiting[b]
2	With a clinical diagnosis of mild dementia due to Alzheimer's disease	Donepezil or galantamine or rivastigmine[b, c]

a. Presented is the respective ACT specified by the G-BA.
b. Non-drug measures as defined in the German Remedies Directive or the Medicines Catalogue (occupational therapy, e.g. cognitive training) should, where appropriate, be offered in both study arms. The type and scope of the interventions used must be documented.
c. Acetylcholinesterase inhibitors (AChEIs) (donepezil, galantamine and rivastigmine) are approved for the symptomatic treatment of mild to moderate Alzheimer's dementia. The aim should be to administer the highest tolerable dose. For the benefit assessment, the on-label use of drugs within the context of a study must be observed.

AChEI: acetylcholinesterase inhibitors; ApoE ε4: apolipoprotein E ε4; GBA: Federal Joint Committee; MCI: mild cognitive impairment

To assess the benefit of lecanemab in adult patients with a clinical diagnosis of mild cognitive impairment (MCI) or mild dementia due to Alzheimer's disease (collectively referred to as early-stage Alzheimer's disease) with confirmed amyloid pathology, who are apolipoprotein E ε4 (ApoE ε4) non-carriers or heterozygotes. This randomized controlled trial (RCT) compared lecanemab with placebo. A detailed description of the CLARITY AD study can be found in dossier assessment A25-111 [1].

Information and analyses subsequently submitted by company (research question 1 and research question 2)

In Module 4A, the company primarily presents the results for the total population of the CLARITY AD study. For the benefit assessment, information on the respective relevant subpopulations as defined by the G-BA's research questions were taken from the subgroup analyses on the characteristic 'ApoE ε4 carrier status according to genotype and use of anticoagulants at baseline' (non-carriers or heterozygotes not using anticoagulants at baseline versus homozygous carriers or use of anticoagulants at baseline) presented in Appendix 4 G (see also A25-111 [1]). However, the presented information on the relevant subpopulations was incomplete. The dossier did not contain any information on patient characteristics, study course (treatment duration and observation periods of patients), responses to the patient-reported outcomes questionnaires, symptomatic amyloid-related imaging abnormalities

(ARIA), further specific adverse events (AEs) or subgroup analyses for the subpopulations relevant to the assessment. No data are available on concomitant therapies at baseline or during the course of the study for the relevant subpopulations.

In its written comments, the company subsequently submitted the following information for the relevant subpopulations [2]:

- Patient characteristics, information on data from the study course and duration of observation and treatment, questionnaire response rates, and details on the proportion and adjustment of concomitant medication during the course of the study
- Stratified analyses of all outcomes in the morbidity and health-related quality of life categories considered in dossier assessment A25-111
- Time-to-event analyses of confirmed deterioration on the Clinical Dementia Rating – Sum of Boxes (CDR-SB)
- Information on symptomatic ARIA events
- Information on common AEs, serious AEs (SAEs) and discontinuation due to AEs
- Subgroup analyses for all outcomes mentioned

The analyses and data mentioned are first assessed below across both subpopulations (taking into account the information provided in the dossier). Where appropriate, the data will be used for the benefit assessment or presented as supplementary information in the relevant Sections 2.1 (relating to research question 1) and 2.2 (relating to research question 2) of this addendum.

Information on the proportion of patients and adjustments of the therapy during the course of the study

Also within the framework of its comments, the company does not provide details regarding the dosage and timing of adjustments to concomitant treatment with acetylcholinesterase inhibitors (AChEIs), nor regarding the duration of such treatment prior to the start of the study. Furthermore, there is still a lack of data on whether treatments were adjusted to optimize therapy or because of a lack of efficacy or progression to the next stage. Nor did the company provide details on the proportion and type of non-drug therapies used during the study.

Time-to-event analyses for the outcome symptoms (CDR-SB)

The dossier assessment described that due to progressive nature of the disease, time-to-event analyses would be preferable in terms of content to analyses at a fixed point in time for outcomes on morbidity and quality of life. In its comments, the company presented time-to-event analyses for the primary and assessment-relevant outcome CDR-SB [2]. A detailed

description of the CDR-SB instrument was provided in dossier assessment A25-111. For the other outcomes of morbidity and quality of life used in the benefit assessment (health status measured with the EQ-5D VAS, cognition using the ADAS-Cog14, and health-related quality of life recorded with the Quality of Life in Alzheimer's Disease Scale [QOL-AD]), the company has not provided any corresponding analyses.

Following the oral hearing, the company subsequently submitted further information regarding the time-to-event analyses for confirmed deterioration, which were submitted during the commenting procedure, as well as analyses of time-to-event analyses for the first deterioration for the CDR-SB [3].

Time-to-event analyses of confirmed deterioration are not suitable for the benefit assessment

For the CDR-SB, the company provided time-to-event analysis on confirmed deterioration by ≥ 2.7 points in its comments. As a general rule, a confirmed (and, where applicable, permanent) deterioration is to be preferred to a first deterioration in the context of this therapeutic indication. This is because a deterioration that persists over a longer period of time is more relevant and maps the progressive course of the disease than isolated deteriorations at specific points in time.

Confirmed deterioration was defined as a deterioration by the response criterion at two consecutive visits. Missing values were not imputed, and a one-off deterioration without a follow-up survey was not classified as a confirmed deterioration. Patients with a first deterioration at Month 18 – that is, at the end of the follow-up period – are not included in the analysis as patients with an event. Patients who experienced a deterioration during the course of the study and for whom no further recordings were subsequently available (e.g. due to study discontinuation) are also not counted as patients with an event. This analysis corresponds to the prespecified analysis for the Clinical Dementia Rating Global Score (CDR-GS); however, given the present data constellation, it is not suitable for the benefit assessment for the following reasons:

- The current observation period for the CDR-SB (18 months) is initially sufficient for consideration in the benefit assessment. Longer follow-up periods would be desirable, particularly in the early stages of the disease. By contrast, however, the analysis on confirmed deterioration considers deterioration up to Month 15 at the latest (with confirmation at Month 18). Deterioration at Month 18 is therefore not included in the analysis as a deterioration, as no follow-up survey is carried out in which this could be confirmed. The time-to-event analyses on first deterioration (see below) clearly show that a relevant proportion of patients did indeed experience their first deterioration at Month 18 and were therefore not included in the analyses on confirmed deterioration (see the

Kaplan-Meier curve on first deterioration at Month 18 in Figure 3 and Figure 5 in Appendix B.1). This clearly shows that it is appropriate to use analyses that consider events up to Month 18 in the current data situation. For research question 2, the high proportion of patients experiencing deterioration at Month 18 in the lecanemab arm is striking in the Kaplan-Meier curve. These are not classified as patients with deterioration in the time-to-event analysis on confirmed deterioration. As a result, the effect estimate of this analysis does not meaningfully reflect the effect of lecanemab on symptom deterioration over the 18-month observation period, but yields a biased result in favour of lecanemab. The company has not presented the sensitivity analyses described by IQWiG during the oral hearing [5] and subsequently requested after the oral hearing, in which patients with a deterioration at Month 18 are classified as an event.

- Any deterioration in the course of the study not entailing a follow-up survey – for example, due to study discontinuation – was not classified as a deterioration in the analysis. In the context of this area of application, it is questionable whether this approach is appropriate, as a progressive course is assumed and, consequently, even a one-off deterioration recorded in the CDR-SB may be relevant. For research question 2, there is also a sharp decline in response rates for the CDR-SB over time, with significant differences between the study arms (see Table 24 in Appendix B.1). The response rates in the lecanemab arm were lower than in the control arm. As a result, deteriorations – particularly in the lecanemab arm – were potentially not taken into account in the analysis of confirmed deterioration, as confirmation could not be obtained due to the lack of a follow-up survey. There is a potential bias in favour of lecanemab in the analyses on confirmed deterioration. The company has not presented the sensitivity analyses described by IQWiG during the oral hearing [5] and subsequently requested after the oral hearing, in which patients with deterioration are included even if follow-up surveys are missing. Nor did the company provide the reasons for censoring.

Uncertainties regarding the time-to-event analyses on first deterioration

The company subsequently submitted time-to-event analyses on first deterioration, which do not correspond to the sensitivity analyses on confirmed deterioration subsequently requested and described above [3]. Although the time-to-event analyses on first deterioration confirm, as described above, the unsuitability of the analyses on confirmed deterioration, they cannot be interpreted with sufficient certainty as a standalone analysis based on the available data. In its supplementary submission, the company refers to the statistical analysis plan of the CLARITY AD study and states that patients who had not experienced an event (a deterioration) by Month 18 were censored. According to the statistical analysis plan, follow-up visits after study discontinuation, as well as visits from the single-arm, open-label extension phase, were not included in the analyses. It is therefore not comprehensible why the analyses submitted as a supplementary submission include censorings at Month 21. It is unclear to what extent

patients with event shortly after Month 18 (but within the visit window) were included in the analysis. Based on the course of the curve, events in the lecanemab arm may not have been considered, particularly in research question 2 (see Figure 5 in Appendix B.1 for research question 2). Consequently, the only marginally statistically significant effect with an upper confidence interval (CI) of 0.998 cannot be interpreted with sufficient certainty.

Summary assessment of the time-to-event analyses

The predefined operationalization of the time to confirmed deterioration is not suitable for the benefit assessment in the present data constellation. This can be learned from the subsequently submitted sensitivity analyses on the first deterioration. The event-time analyses presented on the first deterioration cannot be interpreted with sufficient certainty due to missing information or data that have not been explained in sufficient detail, and are therefore not suitable for the benefit assessment.

Irrespective of this, time-to-event analyses are only available for the primary outcome CDR-SB. The company did not present such analyses for further outcomes on morbidity and health-related quality of life.

The subsequently submitted data on the time-to-event analyses are set out in Appendix B.1 as supplementary information; however, they cannot be interpreted with sufficient certainty and are not suitable for the benefit assessment.

Responder analyses at Month 18 were used for the benefit assessment

As in dossier assessment A25-111, the responder analyses at Month 18 were used to derive the added benefit. The responder analyses for Month 18 presented in dossier assessment A25-111 were based on the unstratified subgroup analyses. As part of the comments, stratified analyses are now available for all outcomes on morbidity and health-related quality of life, and these are preferred for the benefit assessment. However, a comparison of the stratified with the unstratified analyses reveals no difference relevant to the conclusion.

As supplementary information, the continuous analyses are presented for all outcomes on morbidity and health-related quality of life. In the dossier, these were only available from the subgroup analyses for the relevant subpopulations and had already been presented as supplementary information for the CDR-SB during the dossier assessment. In its comments, the company presented prespecified analyses on changes at Month 18 for all outcomes of the categories morbidity and health-related quality of life relevant to the assessment, based on a mixed-effects model with repeated measures (MMRM).

Information on symptomatic ARIA events

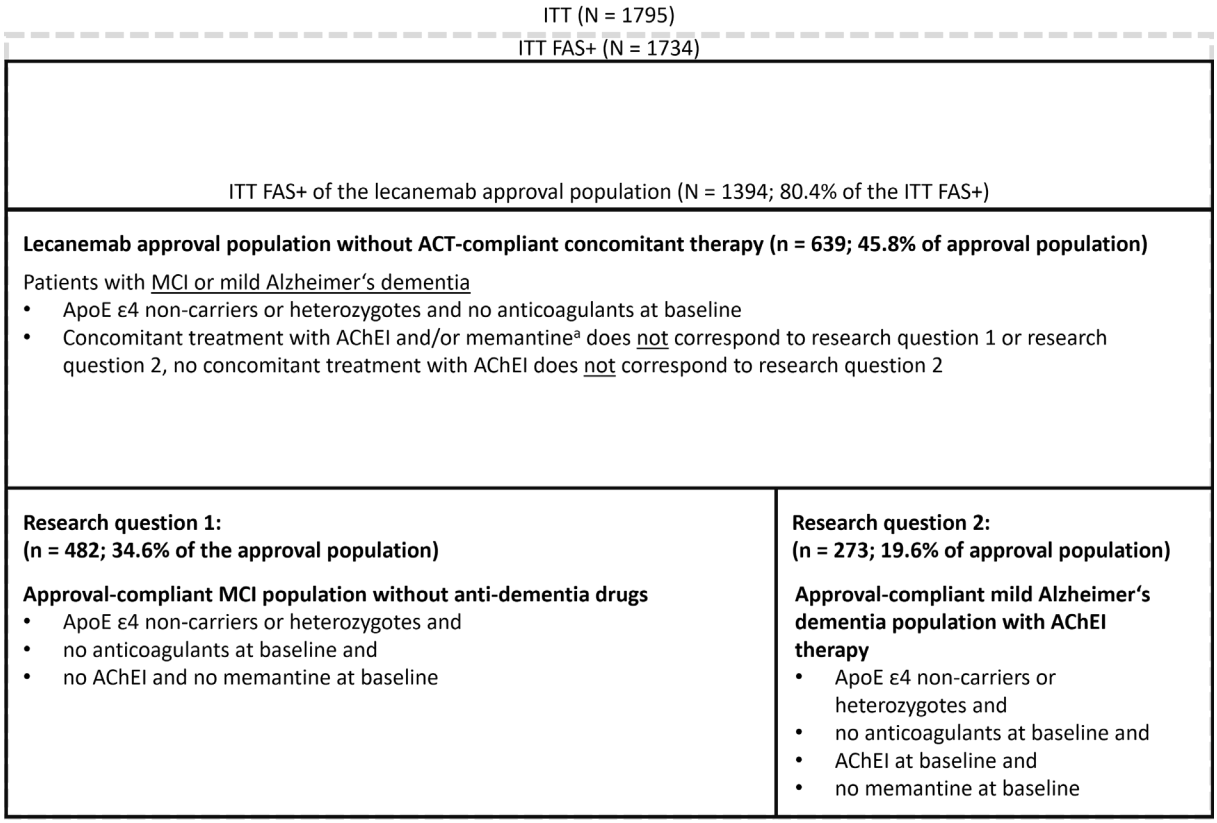
The analyses of symptomatic ARIA events submitted by the company do not include events summarized under the term ‘asymptomatic serious ARIA’. However, SAEs must in any case be

regarded as relevant to the patient and should therefore be included in the analysis. In the present data situation, it can be estimated that the proportion of patients with asymptomatic serious ARIA is negligible (see Table 25 in Appendix D). Therefore, the analyses presented on symptomatic ARIA events are used. This is a combined analysis of the following events: symptomatic amyloid-related imaging abnormalities-oedema/effusion (ARIA-E), symptomatic amyloid-related imaging abnormalities – haemorrhage (ARIA-H), serious symptomatic ARIA-E and serious symptomatic ARIA-H. Further details on symptomatic ARIA-E events and common AEs are provided in Appendix D and Appendix E respectively.

Information on patient numbers in the approval population

In dossier assessment A25-111, the process of forming the subpopulation from the total population of the CLARITY AD study was explained in detail and supported by informative graphs. As part of the commenting procedure, the company corrected the information in Module 4A, Appendix 4 G, relating to the ITT-FAS+ population (patients who received at least one dose of the respective treatment and for whom a baseline value and at least one post-baseline questionnaire evaluation in the CDR were available).

Relevant information had to be extracted from Appendix 4 G for the dossier assessment. In the tables presented there, the number of patients is consistently given as ITT-FAS+. The ITT-FAS+ consists of those patients who received at least one dose of the respective treatment and for whom a baseline value and at least one post-baseline questionnaire evaluation in the CDR were available. The percentages shown in Figure 1 of dossier assessment A25-111 refer to the data for the key results of the CDR-SB responder analysis at Month 18. Figure 1 of dossier assessment A25-111 showing the proportions of the patient populations therefore remains correct with regard to the key results of the CDR-SB responder analysis at Month 18. Due to the high and differential proportion of missing values at Month 18, the patient numbers and percentage distributions differ from those for the ITT-FAS+ in the approval population. Based on the information in the comments, it can be assumed that there were 1394 (rather than 1184) patients in the ITT FAS+ population of the approval population (see also Figure 2 in Appendix A of this addendum). As a result, the proportion of patients who do not correspond to the marketing authorization of lecanemab stands at 20% of the ITT-FAS+ total population (reduced from 32%) (see Figure 1 below). The proportion of patients within the ITT-FAS+ approval population who were not treated in accordance with the ACT is approximately 46% (increased from approximately 36%).



a. In the lecanemab approval population without ACT-compliant concomitant therapy, approximately 21% of patients with MCI due to Alzheimer's disease and approximately 33% of patients with mild Alzheimer's dementia received off-label memantine.

AChEI: acetylcholinesterase inhibitors; ACT: appropriate comparator therapy; ApoE ε4: apolipoprotein E ε4; ITT: randomized patients; ITT FAS+: patients who received at least one dose of the respective treatment and for whom a baseline value and at least one post-baseline questionnaire evaluation within the Clinical Dementia Rating were available; MCI: mild cognitive impairment; N: number of analysed patients

Figure 1: Proportions of the on-label lecanemab subpopulations of the CLARITY AD study

Due to the undifferentiated use of the term ITT-FAS+ in the tables in Module 4A, Annex 4-G, the number of patients considered in the continuous analyses was also understated in the Appendix to dossier assessment A25-111. These figures were also taken from the company's subgroup analyses. The company stated that patients who received at least one dose of the respective treatment and for whom a baseline value and at least one post-baseline questionnaire evaluation in the CDR were available (according to the definition of ITT-FAS+) were considered in the analysis. However, for the ITT-FAS+, the tables show the number of patients for whom data were recorded at Month 18. The results of the continuous analysis of the CDR-SB for the relevant subpopulations with the corrected patient numbers are presented as supplementary information in Section 2.1.2.3 and Section 2.2.2.3 respectively together with the continuous analyses on the other outcomes of morbidity and health-related quality of life. The effect estimates are not affected by this correction.

2.1 Research question 1

Research question 1 considers the patient population of adults with clinical diagnosis of MCI due to Alzheimer's disease without anti-dementia drugs at baseline, who were ApoE ε4 non-carriers or heterozygotes, and who were not using any anticoagulants at baseline in compliance with the marketing authorization.

2.1.1 Study characteristics (specific to research question 1)

2.1.1.1 Patient characteristics

Table 2 shows the characteristics of the patients in the subpopulation of the included study relevant to research question 1.

Table 2: Characteristics of the study population as well as study/treatment discontinuation – RCT, direct comparison: lecanemab versus placebo (research question 1) (multipage table)

Study characteristic category	Lecanemab N[a] = 242	Placebo N[a] = 240
CLARITY AD		
Age [years], mean (SD)	71 (8)	71 (8)
Sex [F/M], %	54/46	53/48
Region (IxRS), n (%)		
North America	152 (63)	160 (67)
Europe (including Australia)	58 (24)	51 (21)
Asia-Pacific	32 (13)	29 (12)
ApoE ε4 carrier status by genotype (laboratory), n (%)		
Heterozygotes	145 (60)	146 (61)
Non-carriers	97 (40)	94 (39)
CDR-GS, n (%)		
0.5 (very mild dementia)	ND[b]	ND[b]
1 (mild dementia)	ND[b]	ND[b]
CDR-SB (score)		
Mean (SD)	2.60 (1.08)	2.68 (1.09)
Median [min; max]	2.50 [0.5; 5.5]	2.50 [0.5; 7]
MMST (score)	ND	ND
ADAS-Cog14		
Mean (SD)	22.12 (6.66)	21.42 (6.94)
Median [min; max]	22.33 [6.7; 45.3]	21.00 [5.7; 44.7]
EQ-5D VAS		
Mean (SD)	82.2 (13.09)	81.2 (13.08)
Median [min; max]	85.0 [39; 100]	81.0 [21; 100]
QOL-AD		
Mean (SD)	39.3 (6.13)	39.4 (6.07)
Median [min; max]	39.0 [19; 52]	39.0 [23; 51]
Age at initial onset of symptoms [years], n (%)		
Mean (SD)	67.6 (8.3)	67.8 (8.0)
Median [min; max]	68.3 [38; 84.4]	68.6 [29.9; 84.3]
Age group at initial onset of symptoms [years], n (%)		
< 30	0	1 (< 1)
30 to < 50	5 (2)	3 (1)
50 to < 65	79 (33)	74 (31)
65 to < 75	109 (45)	116 (48)
≥ 75	49 (20)	46 (19)
Time since initial onset of symptoms [years], mean (SD)		

Table 2: Characteristics of the study population as well as study/treatment discontinuation – RCT, direct comparison: lecanemab versus placebo (research question 1) (multipage table)

Study characteristic category	**Lecanemab N[a] = 242**	**Placebo N[a] = 240**
Mean (SD)	3.9 (2.5)	3.8 (2.8)
Median [min; max]	3.4 [0.5; 21.2]	3.2 [0.5; 25.6]
Age at diagnosis [years], n (%)		
Mean (SD)	70.4 (7.9)	70.7 (7.6)
Median [min; max]	70.8 [50; 85.3]	71.5 [50.4; 89.4]
Age group at diagnosis [years], n (%)		
30 to < 50	0	0
50 to < 65	61 (25)	52 (22)
65 to < 75	101 (42)	116 (48)
≥ 75	80 (33)	70 (29)
Missing	0	2 (1)
Time since diagnosis [years], n (%)		
Mean (SD)	1.1 (1.3)	0.9 (1.1)
Median [min; max]	0.5 [0; 7.7]	0.4 [0; 7.6]
Treatment discontinuation, n (%)[c]	35 (15)	29 (12)
Study discontinuation, n (%)[d]	22 (9)	25 (10)

a. ITT-FAS+: patients who received at least one dose of the respective treatment and for whom a baseline value and at least one post-baseline questionnaire evaluation in the CDR were available.
b. According to the inclusion criteria, patients with MCI must have a CDR-GS of no more than 0.5.
c. Common reasons for treatment discontinuation in the intervention versus the control arm were: withdrawal of consent (5% vs. 5%), AE (3% versus 3%), decision of the patient (3% vs. 1 %). 207 (86%) vs. 211 (88%) of the patients completed treatment as planned.
d. Common reasons for study discontinuation in the intervention versus the control arm were: withdrawal of consent (4% vs. 5%), AE (2% versus 3%), decision of the patient (2% vs. 1%). Furthermore, there were no deaths in the intervention arm. In the control arm, three patients died whilst receiving the study medication.

ADAS-Cog 14: Alzheimer's Disease Assessment Scale – Cognitive subscale (14-item version); ApoE ε4: apolipoprotein E ε4; CDR: Clinical Dementia Rating; CDR-GS: Clinical Dementia Rating-Global Score; CDR-SB: Clinical Dementia Rating-Sum of Boxes; f: female; IxRS: interactive voice/web response system; m: male; MMST: Mini Mental State Examination; n: number of patients in the category; N: number of analysed patients (ITT-FAS+); ND: no data; QOL-AD: Quality of Life in Alzheimer's Disease Scale; RCT: randomized controlled trial; SD: standard deviation

The mean age of the patients was around 71 years; most of them were of European or North American family origin. The proportion of men and women was largely balanced. On average, the first symptoms appeared in patients just under four years prior to study inclusion.

At the start of the study, the patients had a CDR-SB (scale from 0 to 18) of 2.6 and 2.7 respectively. At baseline, the scores on the ADAS-Cog14 assessment scale for Alzheimer's

disease were 22 or 21 respectively, on a scale ranging from 0 to 90, with higher scores indicating more severe cognitive impairment. The QOL-AD scores for the recording of the quality of life in individuals with Alzheimer's disease (scale from 13 to 52) averaged 39 for both study arms, with higher scores indicating a better quality of life. No data on CDR-GS or mini mental status test (MMST) at baseline are available for the populations described, although these were defined as inclusion criteria for the study.

Over the course of the study, more patients in the intervention arm discontinued treatment prematurely than in the control arm (15% vs. 12%). Common reasons for treatment discontinuation were withdrawal of consent, AEs and patient decision. The majority of patients who discontinued treatment also discontinued the study (9% vs. 10%).

Overall, the demographic and clinical characteristics of the patients included are considered to be sufficiently comparable.

Concomitant treatments

The data on concomitant treatments at baseline and in the course of the study are presented in Table 3.

Table 3: Concomitant medication in the course of the study – RCT, direct comparison: lecanemab versus placebo (research question 1)

Study	**Patients with anti-dementia treatment, n (%)**	
	Lecanemab	**Placebo**
CLARITY AD	N[a] = 242	N[a] = 240
Commencement of treatment with anti-dementia drugs during the study[b]	32 (13)	24 (10)
Donepezil	22 (9)	20 (8)
Galantamine	5 (2)	0 (0)
Memantine	3 (1)	2 (1)
Rivastigmine	8 (3)	4 (2)

a. ITT-FAS+: patients who received at least one dose of the respective treatment and for whom a baseline value and at least one post-baseline questionnaire evaluation in the CDR were available.
b. Patients were able to take several drugs.

CDR: Clinical Dementia Rating; n: number of patients in the category; N: number of analysed patients; RCT: randomized controlled trial

During the course of the study, concomitant treatment with anti-dementia drugs was initiated in approximately 13 per cent of patients in the intervention arm and 10 per cent of patients in the control arm, mostly with donepezil. A small proportion of patients began treatment with memantine, which is only approved for use from the stage of moderate dementia onwards. The proportion is considered to be negligible.

Overall, the concomitant medication was sufficiently comparable in both study arms. However, details regarding the dosage and the reasons for adjusting the treatment are still missing. Information on non-drug treatments is also still lacking.

Treatment duration and observation period

Table 4 shows the mean and median treatment duration of the patients as well as the mean and median observation period for individual outcomes.

Table 4: Information on the course of the study – RCT, direct comparison: lecanemab versus placebo (research question 1)

Study	**CLARITY AD**	
duration of the study phase **outcome category/outcome**	**Lecanemab**	**Placebo**
Treatment duration [months]	N = 252	N = 245
Median [min; max]	18.0 [0.5; 18.7]	18.0 [0.5; 18.5]
Mean (SD)	16.4 (4.4)	16.9 (3.5)
Observation period [months]		
All-cause mortality[a, b]	N = 252	N = 245
Median [Q1; Q3]	17.0 [16.9; 17.2]	17.0 [16.9; 17.2]
Mean (SD)	15.7 (4.1)	16.2 (3.3)
Morbidity	N = 242	N = 240
Symptoms (CDR-SB)[c]		
Median [Q1; Q3]	18.0 [17.9; 18.2]	18.0 [17.9; 18.2]
Mean (SD)	17.2 (3.0)	17.2 (3.1)
Cognition (ADAS-Cog14)[c]		
Median [Q1; Q3]	18.0 [17.9; 18.2]	18.0 [17.9; 18.2]
Mean (SD)	17.2 (3.0)	17.1 (3.1)
Health status (EQ-5D VAS)[c]		
Median [Q1; Q3]	18.0 [17.9; 18.2]	18.0 [17.9; 18.2]
Mean (SD)	17.0 (3.5)	17.0 (3.6)
Health-related quality of life (QOL-AD)[c]	N = 242	N = 240
Median [Q1; Q3]	18.0 [17.9; 18.2]	18.0 [17.9; 18.2]
Mean (SD)	17.0 (3.5)	17.0 (3.6)
Side effects[b]	N = 252	N = 245
Median [Q1; Q3]	17.0 [16.9; 17.2]	17.0 [16.9; 17.2]
Mean (SD)	15.7 (4.1)	16.2 (3.3)

a. All-cause mortality was recorded as fatal adverse event.
b. According to the company, AEs were defined as any event occurring during treatment or within 30 days of the last dose of the study medication.
c. The observation period is defined as the time from randomization to the last recording with the respective instrument (without follow-up visit).

ADAS-Cog 14: Alzheimer's Disease Assessment Scale – Cognitive subscale (14-item version); CDR-SB: Clinical Dementia Rating-Sum of Boxes; max: maximum; min: minimum; N: number of analysed patients; Q1: 1st quartile; Q3: 3rd quartile; QOL-AD: Quality of Life in Alzheimer's Disease Scale; RCT: randomized controlled trial; SD: standard deviation; VAS: visual analogue scale

During the RCT phase of the CLARITY AD study, the mean treatment duration of patients in the intervention and the control arm was 16 and 17 months respectively. The average follow-up period for the outcomes of the categories morbidity and health-related quality of life was

17 months in both study arms. The outcomes of the side effects category and all-cause mortality were observed for an average of 16 months during the RCT phase.

Overall, treatment duration and observation periods are considered to be sufficiently comparable between the study arms.

2.1.2 Results on added benefit

2.1.2.1 Outcomes included

The outcomes used for the benefit assessment are described in dossier assessment A25-111 [1].

Table 5 shows for which outcomes data were available in the included study.

Table 5: Matrix of outcomes – RCT, direct comparison: lecanemab versus placebo (research question 1)

Study	Outcomes											
	All-cause mortality[a]	Symptoms (CDR-SB)	Cognition (ADAS-Cog14)	Independence in everyday life	Behavioural changes	Health status (EQ-5D VAS)	Health-related quality of life (QOL AD)	SAEs	Discontinuation due to AEs	Symptomatic ARIA events[b]	Infusion related reactionc (AEs)	Other specific AEs
CLARITY AD	Yes	Yes	Yes	No[d]	No[d]	Yes	Yes	Yes	Yes	Yes	Yes	No[e]

a. The results on all-cause mortality are based on the information on fatal AEs.
b. The following events are considered: symptomatic ARIA-E, symptomatic ARIA-H, serious ARIA-E and serious ARIA-H.
c. Operationalized via a PT list compiled by the company; for further details, see dossier assessment A25-111, Section I 4.2.1 [1].
d. No suitable data available; for justification see dossier assessment A25-111, Section I 4.2.1 [1].
e. No further specific AEs were identified based on the AEs occurring in the relevant study.

ADAS-Cog 14: Alzheimer's Disease Assessment Scale – Cognitive Subscale, 14-item version; AE: adverse event; ARIA-E: amyloid-related imaging abnormalities-oedema/effusion; ARIA-H: amyloid-related imaging abnormalities – haemorrhage; CDR-SB: Clinical Dementia Rating-Sum of Boxes; PT: Preferred Term; QOL-AD: Quality of Life in Alzheimer's Disease Scale; RCT: randomized controlled trial; SAE: serious adverse event; VAS: visual analogue scale

2.1.2.2 Risk of bias and certainty of conclusions

In dossier assessment A25-111 [1], the risk of bias across outcomes was rated as low.

Table 6 shows the risk of bias for CLARITY AD at outcome level.

Table 6: Risk of bias across outcomes and outcome-specific risk of bias – RCT, direct comparison: lecanemab versus placebo (research question 1)

Study	Study level	Outcomes										
		All-cause mortality[a]	Symptoms (CDR-SB)	Cognition (ADAS-Cog14)	Independence in everyday life	Behavioural changes	Health status (EQ-5D VAS)	Health-related quality of life (QOL AD)	SAEs	Discontinuation due to AEs	Symptomatic ARIA events[b]	Infusion related reactionc (AEs)
CLARITY AD	L	L	H[d]	H[d]	–[e]	–[e]	H[d]	H[d]	L	L	L	L

a. The results on all-cause mortality are based on the information on fatal AEs.
b. The following events are considered: symptomatic ARIA-E, symptomatic ARIA-H, serious ARIA-E and serious ARIA-H.
c. Operationalized via a PT list compiled by the company; for further details, see dossier assessment A25-111, Section I 4.2.1 [1].
d. High proportion of patients not included in the analysis (> 10%) and large difference between the treatment groups (> 5 percentage points).
e. No suitable data available; for justification see dossier assessment A25-111, Section I 4.2.1 [1].

ADAS-Cog 14: Alzheimer's Disease Assessment Scale – Cognitive Subscale, 14-item version; ARIA-E: amyloid-related imaging abnormalities-oedema/effusion; ARIA-H: amyloid-related imaging abnormalities – haemorrhage; CDR-SB: Clinical Dementia Rating-Sum of Boxes; H: high; L: low; PT: Preferred Term; QOL-AD: Quality of Life in Alzheimer's Disease Scale; RCT: randomized controlled trial; SAE: serious adverse event; VAS: visual analogue scale

As part of the commenting procedure, the company submitted new data on the study course and on treatment and study discontinuations. The risk of bias of the outcomes overall survival and side effects was rated as low. For all outcomes in the categories morbidity and health-related quality of life, the company provided information on response rates in its comments. The data presented show a high proportion of patients not included in the analysis (> 10%) and a large difference between the treatment groups (> 5 percentage points). The assessment of the risk of bias for the outcomes in the categories morbidity and health-related quality of life described in dossier assessment A25-111 therefore remains unchanged. The risk of bias is still rated as high for these outcomes.

Dossier assessment A25-111 described further aspects that led to a reduction in the certainty of conclusions: a lack of guidelines on how to deal with a lack of efficacy or progression to the next stage, as well as a lack of data on non-drug therapies. In its comments, the company has

not provided the data required to assess these further aspects. The certainty of conclusions therefore remains restricted. At most hints, e.g. of an added benefit, can be derived.

2.1.2.3 Results

Table 7 and Table 8 summarize the results subsequently submitted from the comparison of lecanemab with placebo in patients with MCI due to Alzheimer's disease without anti-dementia drugs at baseline, who are ApoE ε4 non-carriers or heterozygotes, and who were not using any anticoagulants at baseline. Unlike in the dossier assessment, stratified analyses are now available for the outcomes of the categories morbidity and health-related quality of life. Where necessary, calculations conducted by the Institute are provided in addition to the data from the company's comments.

Tables on common AEs, common SAEs and discontinuations due to AEs are presented in Appendix E.1.

Further details on symptomatic ARIA events are set out in Appendix D.

Table 7: Results (mortality, morbidity, health-related quality of life, side effects, dichotomous) – RCT, direct comparison: lecanemab versus placebo (research question 1) (multipage table)

Study outcome category outcome	Lecanemab N	Lecanemab patients with event n (%)	Placebo N	Placebo patients with event n (%)	Lecanemab vs. placebo RR [95% CI];p-value
CLARITY AD					
Mortality					
All-cause mortality[a]	252	0 (0)	245	3 (1.2)	0.14 [0.01; 2.68]; 0.080[b]
Morbidity					
Symptoms (CDR-SB – deterioration at Month 18[c])	216	22 (10.2)	217	25 (11.5)	0.85 [0.51; 1.44]; 0.547[d]
Cognition (ADAS-Cog14 – deterioration at Month 18[e])	213	11 (5.2)	215	12 (5.6)	0.86 [0.39; 1.89]; 0.705[d]
Independence in everyday life				No suitable data[f]	
Behavioural changes				No suitable data[f]	
Health status (EQ-5D VAS – deterioration at Month 18[g])	216	37 (17.1)	218	36 (16.5)	1.02 [0.67; 1.55]; 0.923[d]
Health-related quality of life					
QOL-AD (deterioration at Month 18[h])	216	21 (9.7)	217	21 (9.7)	1.00 [0.57; 1.78]; 0.992[d]
Side effects					
AEs (supplementary information)[o]	252	226 (89.7)	245	207 (84.5)	–
SAEs[i]	252	37 (14.7)	245	28 (11.4)	1.28 [0.81; 2.03]; 0.293[b]
Discontinuation due to AEs	252	11 (4.4)	245	7 (2.9)	1.53 [0.60; 3.88]; 0.530[b]
Symptomatic ARIA events[j]	252	6 (2.4)	245	0 (0)	12.64 [0.72; 223.18]; 0.016[b]
Infusion related reaction (AE)[k]	252	67 (26.6)	245	19 (7.8)	3.43 [2.13; 5.53]; < 0.001[b]

a. The results on all-cause mortality are based on the information on fatal AEs.
b. Effect and CI: unstratified logistic regression model; p-value: Institute's calculation (unconditional exact test [CSZ method according to [6]).
c. An increase of the CDR-SB by ≥ 2.7 points (15% of the scale range) from baseline is considered a clinically relevant deterioration (score range of the scale: 0 to 18).
d. Effect, CI and p-value: logistic regression model stratified by subpopulation, AChEI use at baseline, ApoE-ε4 status and region.
e. An increase by ≥ 13.5 points (15% of the scale range) from baseline is considered a clinically relevant deterioration (score range of the scale 0 and 90).
f. For justification see Section I 4.2.1 of dossier assessment A25-111 [1].
g. A decrease by ≥ 15 points (15% of the scale range) from baseline is considered a clinically relevant deterioration (score range of the scale: 0 to 100).
h. A decrease by ≥ 5.85 points (15% of the scale range) from baseline is considered a clinically relevant deterioration (score range of the scale: 13 to 52).
i. With the exclusion of disease-related events (see Section I 4.2.1 of dossier assessment A25-111 [1]).
j. The following events are considered: symptomatic ARIA-E, symptomatic ARIA-H, serious ARIA-E and serious ARIA-H (see also Table 25 in Appendix D).
k. Operationalized via a PT list compiled by the company (see dossier assessment A25-111, Section I 4.2.1 [1]).

Table 7: Results (mortality, morbidity, health-related quality of life, side effects, dichotomous) – RCT, direct comparison: lecanemab versus placebo (research question 1) (multipage table)

Study outcome category outcome	Lecanemab N	Lecanemab patients with event n (%)	Placebo N	Placebo patients with event n (%)	Lecanemab vs. placebo RR [95% CI];p-value
AChEI: acetylcholinesterase inhibitors; ADAS-Cog 14: Alzheimer's Disease Assessment Scale – Cognitive Subscale, 14-item version; AE: adverse event; ARIA: amyloid-related imaging abnormalities; ARIA-E: amyloid-related imaging abnormalities-oedema/effusion; ARIA-H: amyloid-related imaging abnormalities – haemorrhage; CDR-SB: Clinical Dementia Rating-Sum of Boxes; CI: confidence interval; n: number of patients with (at least one) event; N: number of analysed patients; QOL-AD: Quality of life in Alzheimer's Disease Scale; RCT: randomized controlled trial; RR: relative risk SAE: serious adverse event; VAS: visual analogue scale					

Table 8: Results (morbidity, continuous, supplementary presentation) – RCT, direct comparison: lecanemab vs. placebo (research question 1)

Study outcome category outcome	Lecanemab N[a]	Lecanemab values at baseline mean (SD)	Lecanemab change at month 18 mean[b] (SE)	Placebo N[a]	Placebo values at baseline mean (SD)	Placebo change at month 18 mean[b] (SE)	Lecanemab ± AChEI vs. placebo ± AChEI mean difference [95% CI][b]; p-value
CLARITY AD							
Morbidity							
Symptoms (CDR-SB)[c]	242	2.6 (1.07)	0.92 (0.12)	240	2.7 (1.09)	1.05 (0.12)	-0.13 [-0.47; 0.20]; 0.434
Cognition (ADAS-Cog14)[d]	240	22.1 (6.7)	3.13 (0.51)	240	21.4 (6.9)	3.13 (0.51)	-0.01 [-1.36; 1.35]; < 0.994
Health status (EQ-5D VAS)[e]	238	82.2 (13.1)	-2.66 (0.92)	236	81.2 (13.1)	-3.98 (0.93)	1.32 [-1.08; 3.72]; 0.281
Health-related quality of life							
QOL-AD[f]	238	39.3 (6.1)	-0.72 (0.28)	236	39.4 (6.1)	-1.00 (0.29)	0.28 [-0.45; 1.01]; 0.453

a. Number of patients considered in the effect estimation.
b. MMRM analysis with treatment group, region, visit, subpopulation, ApoE-ε4 status, AChEI use at baseline, baseline value, interactions treatment group*visit and baseline value*visit.
c. Lower (decreasing) values indicate improved symptoms; negative effects (intervention minus comparison) indicate an advantage of the intervention (scale range: 0 to 18).
d. Lower (decreasing) values indicate improved symptoms; negative effects (intervention minus comparison) indicate an advantage of the intervention (scale range: 0 to 90).
e. Higher (increasing) values indicate better health status; positive effects (intervention minus comparison) indicate an advantage for the intervention (scale range: 0 to 100).
f. Higher (increasing) values indicate better health-related quality of life; positive effects (intervention minus comparison) indicate an advantage for the intervention (scale range: 13 to 52).

ADAS-Cog 14: Alzheimer's Disease Assessment Scale – Cognitive Subscale, 14-item version; CDR-SB: Clinical Dementia Rating-Sum of Boxes; CI: confidence interval; MMRM: mixed-effects model with repeated measures; N: number of analysed patients; QOL-AD: Quality of Life in Alzheimer's Disease Scale; RCT: randomized controlled trial; SD: standard deviation; SE: standard error; SMD: standardized mean difference

Based on the available information, at most hints, e.g. of an added benefit, can be determined for all data subsequently submitted with the comments (see Section 2.1.2.2 of this addendum for reasoning).

Mortality

All-cause mortality

No statistically significant difference between treatment groups was found for the outcome of all-cause mortality. There is no hint of an added benefit of lecanemab in comparison with watchful waiting; an added benefit is therefore not proven.

Morbidity

Symptoms (CDR-SB)

No statistically significant difference between treatment groups was found for the outcome of symptoms (recorded using the CDR-SB). There is no hint of an added benefit of lecanemab in comparison with watchful waiting; an added benefit is therefore not proven.

The continuous analyses presented as supplementary information also show no statistically significant difference between treatment groups.

Cognition (ADAS-Cog14)

No statistically significant difference between treatment groups was found for the outcome cognition, recorded using the ADAS-Cog14). There is no hint of an added benefit of lecanemab in comparison with watchful waiting; an added benefit is therefore not proven.

The continuous analyses presented as supplementary information also show no statistically significant difference between treatment groups.

Independence in everyday life

No suitable data were available for the outcome independence in everyday life (see Section I 4.2.1 of dossier assessment A25-111 for reasoning). There is no hint of an added benefit of lecanemab in comparison with watchful waiting; an added benefit is therefore not proven.

Behavioural changes

No suitable data were available for the outcome behavioural changes (see Section I 4.2.1 of dossier assessment A25-111 for reasoning). There is no hint of an added benefit of lecanemab in comparison with watchful waiting; an added benefit is therefore not proven.

Health status (EQ-5D VAS)

For the outcome of health status, recorded using the EQ-5D VAS, no statistically significant difference was found between treatment groups. There is no hint of an added benefit of lecanemab in comparison with watchful waiting; an added benefit is therefore not proven.

The continuous analyses presented as supplementary information also show no statistically significant difference between treatment groups.

Health-related quality of life (QOL AD)

No statistically significant difference between treatment groups was found for the outcome health-related quality of life, recorded using the QOL-AD. There is no hint of an added benefit of lecanemab in comparison with watchful waiting; an added benefit is therefore not proven.

The continuous analyses presented as supplementary information also show no statistically significant difference between treatment groups.

Side effects

SAEs and discontinuation due to AEs

No statistically significant difference between treatment groups was found for either of the outcomes SAEs or discontinuation due to AEs. There is no hint of greater or lesser harm from lecanemab in comparison with watchful waiting; greater or lesser harm is therefore not proven.

Symptomatic ARIA events

A statistically significant difference to the disadvantage of lecanemab compared with watchful waiting was shown for the outcome symptomatic ARIA events. There is a discrepancy between the CI and the p-value. The difference is therefore no more than marginal for this outcome in the category non-serious/non-severe side effects in the subpopulation under consideration (see also Section 2.1.3.1). There was no hint of greater or lesser harm from lecanemab in comparison with watchful waiting; greater or lesser harm is therefore not proven.

Infusion related reaction (AEs)

A statistically significant difference to the disadvantage of lecanemab compared with watchful waiting was shown for the outcome infusion-related reactions (AEs). There was a hint of greater harm from lecanemab in comparison with watchful waiting.

2.1.2.4 Subgroups and other effect modifiers

The following potential effect modifiers were considered for the present benefit assessment:

- Sex (male versus female)
- Age (< 65 years versus ≥ 65 and < 75 years versus ≥ 75 years)

Subgroup analyses of the 2 characteristics mentioned were planned a priori.

Interaction tests are performed when at least 10 patients per subgroup are included in the analysis. For binary data, there must also be at least 10 events in at least one subgroup.

Only the results with an effect modification with a statistically significant interaction between treatment and subgroup characteristic (p-value < 0.05) are presented. In addition, subgroup results are only presented if there is a statistically significant and relevant effect in at least one subgroup.

Using the methods described above, the available subgroup analyses did not reveal any effect modifications.

2.1.3 Probability and extent of added benefit

The probability and extent of added benefit at outcome level are derived below, taking into account the different outcome categories and effect sizes. The methods used for this purpose are explained in the *General Methods* of IQWiG [7].

The approach for deriving an overall conclusion on the added benefit based on the aggregation of conclusions derived at outcome level is a proposal by IQWiG. The G-BA decides on the added benefit.

2.1.3.1 Assessment of added benefit at outcome level

The extent of the respective added benefit at outcome level was assessed based on the results presented in Section 2.1.2.3 (see Table 9).

Determination of the outcome category for the outcome symptomatic ARIA events

The following events are considered for the outcome symptomatic ARIA events: symptomatic ARIA-E, symptomatic ARIA-H, serious ARIA-E and serious ARIA-H. The data subsequently submitted as part of the commenting procedure show that the outcome predominantly includes non-serious ARIA. Therefore, the outcome was assigned to the outcome category non-serious/non-severe side effects.

Table 9: Extent of added benefit at outcome level: lecanemab versus watchful waiting (research question 1) (multipage table)

Outcome category **outcome**	**Lecanemab vs. placebo** **proportion of events (%)** **effect estimation [95% CI];** **p-value** **probability**[a]	**Derivation of extent**[b]
Mortality		
All-cause mortality	0% vs. 1.2% RR: 0.14 [0.01; 2.68]; p = 0.080	Lesser benefit not proven/added benefit not proven
Morbidity		
Symptoms (CDR-SB – deterioration at Month 18)	10.2% vs. 11.5% RR: 0.85 [0.51; 1.44]; p = 0.547	Lesser benefit not proven/added benefit not proven
Cognition (ADAS-Cog14 – deterioration at Month 18)	5.2% vs. 5.6% RR: 0.86 [0.39; 1.89]; p = 0.705	Lesser benefit not proven/added benefit not proven
Independence in everyday life	No suitable data	Lesser benefit not proven/added benefit not proven
Behavioural changes	No suitable data	Lesser benefit not proven/added benefit not proven
Health status (EQ-5D VAS – deterioration at Month 18)	17.1% vs. 16.5% RR: 1.02 [0.67; 1.55]; p = 0.923	Lesser benefit not proven/added benefit not proven
Health-related quality of life		
QOL-AD (deterioration at Month 18)	9.7% vs. 9.7% RR: 1.00 [0.57; 1.78]; p = 0.992	Lesser benefit not proven/added benefit not proven
Side effects		
SAEs	14.7% vs. 11.4% RR: 1.28 [0.81; 2.03]; p = 0.293	Greater/lesser harm not proven
Discontinuation due to AEs	4.4% vs. 2.9% RR: 1.53 [0.60; 3.88]; p = 0.530	Greater/lesser harm not proven
Symptomatic ARIA events	2.4% vs. 0% RR: 12.64 [0.72; 223.18] RR: 0.08 [0.004; 1.39][c]; p = 0.016	Outcome category: non-serious/non-severe symptoms/late complications $1 < CI_u$, $p < 0.05$ lesser benefit/added benefit not proven[d]

Table 9: Extent of added benefit at outcome level: lecanemab versus watchful waiting (research question 1) (multipage table)

Outcome category **outcome**	**Lecanemab vs. placebo** **proportion of events (%)** **effect estimation [95% CI];** **p-value** **probability**[a]	**Derivation of extent**[b]
Infusion-related reaction (AE)	26.6% vs. 7.8% RR: 3.43 [2.13; 5.53] RR: 0.29 [0.18; 0.47][c]; p < 0.001 probability: hint	Outcome category: non-serious/non-severe side effects CI_u < 0.80 greater harm, extent: considerable

a. Probability provided if there is a statistically significant and relevant effect.
b. Depending on the outcome category, the effect size is estimated using different limits based on the upper limit of the confidence interval (CI_u).
c. Institute's calculation; inverse direction of effect to enable use of limits to derive the extent of the added benefit.
d. Discrepancy between CI and p-value. The result of the statistical test (p-value) is decisive for the derivation of the added benefit. The extent of the effect in this non-serious/non-severe outcome was no more than marginal.

ADAS-Cog 14: Alzheimer's Disease Assessment Scale – Cognitive Subscale, 14-item version; AE: adverse event; ARIA: amyloid-related imaging abnormalities; CDR-SB: Clinical Dementia Rating – Sum of Boxes; CI: confidence interval; CI_u: upper limit of the confidence interval; ND: no data; QOL-AD: Quality of life in Alzheimer's Disease; SAE: serious adverse event; VAS: visual analogue scale

2.1.3.2 Overall conclusion on added benefit

Table 10 summarizes the results taken into account for the overall conclusion on the extent of the added benefit.

Table 10: Positive and negative effects from the assessment of lecanemab in comparison with watchful waiting (research question 1)

Positive effects	**Negative effects**
–	Non-serious/non-severe side effects ▪ infusion related reaction (AE): hint of greater harm – extent "considerable"
No data are available for the outcomes independence in everyday life and behavioural changes.	
AE: adverse event	

Taking into account the analyses subsequently submitted in the commenting procedure, a negative effect was shown for research question 1 in the category non-serious/non-severe side effects based on a specific AE (infusion-related reactions); extent: "considerable".

For symptomatic ARIA events there is a CI covering the zero effect, meaning that no relevant effect was observed in the relevant subpopulation (see also Figure 22). No further specific AEs

were identified. No relevant effect modification was shown in the subgroup characteristics age and sex.

Contextualisation of the overall conclusion before the background of the commenting procedure

With regard to the criticism expressed during the commenting procedure concerning the use of the 15% criterion in this therapeutic indication, it should be emphasized that the continuous analyses presented as supplementary information also show no statistically significant difference between the treatment groups for any of the outcomes in the relevant subpopulation.

With regard to the criticism expressed during the commenting procedure concerning the consideration of the subpopulations in accordance with the G-BA's research questions, it should be emphasized that an overall consideration of the forest plots of the various populations yields an even more vivid pattern in the outcomes in the categories morbidity and health-related quality of life (see Figure 14 to Figure 19 in Appendix C) already described in dossier assessment A25-111. When considering the patients classified as having MCI, it becomes apparent that subpopulations within the approval population who were not treated in accordance with the G-BA's research questions (i.e. who received AChEIs or memantine, each labelled 'not ACT-compliant' in the forest plot) are key to the significant, positive effects of lecanemab in the approval population. This pattern is not only shown in the responder analyses, but also in the continuous analysis on the CDR-SB (see Figure 16), and has already been described in the Health Technology Assessment (HTA) process of the National Institute for Health and Care Excellence (NICE) [8,9]. The respective effect estimates do not lie one below the other; compared with the approval-compliant population they rather shift towards a zero effect for the population receiving the ACT, and towards an effect in favour of lecanemab for MCI patients treated with AChEIs or memantine. As described in dossier assessment A25-111, a greater proportion of events in the control arm appears to be a key factor in this. During the commenting procedure, the company has not subsequently submitted any information on the characteristics of the subpopulation of MCI patients treated with AChEIs or memantine, which might have made it possible to determine the extent to which this patient group differs from the group without AChEIs or memantine.

Irrespective of this, it should be noted that with regard to the significant positive effects of lecanemab in the approval population, significant effects in favour of lecanemab were observed only in the CDR-SB and the ADAS-Cog14 (based on the stratified evaluations in the responder analyses); these (depending on the determination of an outcome category) would, at most, be classified as minor or mild and would need to be weighed against several relevant side effects (see below). It should also be emphasized that the continuous analyses for the CDR-SB show a significant but, when considering the standardized mean difference (SMD),

non-relevant difference also in the approval population, as the 95% CI of the effect is not entirely outside the irrelevance threshold of [−0.2; 0.2] (see also Figure 9 and Figure 16).

By contrast, the forest plots on side effects (see Figure 20 to Figure 23 in Appendix C) show that the effect estimates for the various populations largely lie one below the other, and that only the width of the CI changes when subpopulations are considered. Therefore, comparable disadvantages can be assumed in terms of side effects in the relevant subpopulations compared with the approval population, particularly in the case of symptomatic ARIA. In the approval population or the pooled population from research questions 1 and 2, there is a relevant extent of disadvantages for other outcomes on side effects in addition to infusion-related reactions (symptomatic ARIA and/or discontinuation due to AEs).

With regard to the data from the open-label extension phase of the CLARITY AD study discussed at the oral hearing, it should be noted that the company has still not submitted these data in a form compliant with the dossier template also within the framework of the commenting procedure, meaning that they cannot be assessed due to missing information.

Summary

In summary, for patients with clinically diagnosed MCI due to Alzheimer's disease who are ApoE ε4 non-carriers or heterozygotes, there was no hint of added benefit from lecanemab compared with the ACT. An added benefit is therefore not proven.

2.2 Research question 2

Research question 2 considers the patient population of adults with clinical diagnosis of mild Alzheimer's dementia and treatment with AChEI at baseline who were ApoE ε4 non-carriers or heterozygotes, and who were not using any anticoagulants at baseline.

2.2.1 Study characteristics (specific to research question 2)

2.2.1.1 Patient characteristics

Table 11 shows the characteristics of the patients in the subpopulation of the included study relevant to research question 2.

Table 11: Characteristics of the study population as well as study/treatment discontinuation – RCT, direct comparison: lecanemab + AChEI versus placebo + AChEI (research question 2) (multipage table)

Study characteristic category	**Lecanemab + AChEI N[a] = 136**	**Placebo + AChEI N[a] = 137**
CLARITY AD		
Age [years], mean (SD)	72 (8)	69 (9)
Sex [F/M], %	50/50	50/50
Region (IxRS), n (%)		
North America	63 (46)	56 (41)
Europe (including Australia)	42 (31)	52 (38)
Asia-Pacific	31 (23)	29 (21)
ApoE ε4 carrier status by genotype (laboratory), n (%)		
Heterozygotes	91 (67)	92 (67)
Non-carriers	45 (33)	45 (33)
CDR-GS, n (%)		
0.5 (very mild dementia)	ND[b]	ND[b]
1 (mild dementia)	ND[b]	ND[b]
CDR-SB (score)		
Mean (SD)	3.67 (1.29)	3.73 (1.38)
Median [min; max]	3.50 [1; 8]	3.50 [1; 8.5]
MMST (score)	ND	ND
ADAS-Cog14		
Mean (SD)	27.31 (6.86)	26.95 (7.90)
Median [min; max]	26.84 [7.3; 46.0]	26.00 [7.7; 60.7]
EQ-5D VAS		
Mean (SD)	83.9 (11.87)	80.0 (14.97)
Median [min; max]	84.0 [50; 100]	80.0 [31; 100]
QOL-AD		
Mean (SD)	39.3 (6.06)	38.3 (6.47)
Median [min; max]	39.0 [23; 51]	38.0 [19; 52]
Age at initial onset of symptoms [years], n (%)		
Mean (SD)	68.4 (8.6)	65.5 (9.3)
Median [min; max]	69.2 [45.7; 85.4]	66.6 [45.1; 86.9]
Age group at initial onset of symptoms [years], n (%)		
< 30	0	0
30 to < 50	5 (4)	4 (3)
50 to < 65	33 (24)	55 (40)
65 to < 75	64 (47)	55 (40)
≥ 75	34 (25)	23 (17)

Table 11: Characteristics of the study population as well as study/treatment discontinuation – RCT, direct comparison: lecanemab + AChEI versus placebo + AChEI (research question 2) (multipage table)

Study characteristic category	**Lecanemab + AChEI N[a] = 136**	**Placebo + AChEI N[a] = 137**
Time since initial onset of symptoms [years], mean (SD)		
Mean (SD)	4.1 (2.2)	4.4 (2.6)
Median [min; max]	3.7 [0.6; 11.3]	4.0 [1.2; 15.4]
Age at diagnosis [years], n (%)		
Mean (SD)	70.9 (8.4)	68.4 (9.0)
Median [min; max]	72.0 [51.2; 87.6]	70.2 [49.1; 89.4]
Age group at diagnosis [years], n (%)		
30 to < 50	0	1 (1)
50 to < 65	29 (21)	49 (36)
65 to < 75	57 (42)	49 (36)
≥ 75	50 (37)	38 (28)
Missing	0	0
Time since diagnosis [years], n (%)		
Mean (SD)	1.6 (1.6)	1.5 (1.7)
Median [min; max]	1.0 [0; 9.1]	0.9 [0.1; 11.1]
Treatment discontinuation, n (%)[c]	29 (21)	23 (17)
Study discontinuation, n (%)[d]	29 (21)	22 (16)

a. ITT-FAS+: patients who received at least one dose of the respective treatment and for whom a baseline value and at least one post-baseline questionnaire evaluation in the CDR were available.
b. In the subpopulation of patients with mild Alzheimer's dementia (without consideration of treatment at baseline, ApoE ε4 carrier status and use of anticoagulants), 50% in the intervention arm vs. 50% in the control arm had a CDR-GS of 0.5, whilst 49% in the intervention vs. 51% in the control arm had a CDR-GS of 1.0; Institute's calculation.
c. Common reasons for treatment discontinuation in the intervention versus the control arm were: withdrawal of consent (6% vs. 7%), AE (6% versus 2%), decision of the patient (4% vs. 6%). 107 (79%) vs. 114 (83%) of the patients completed treatment as planned.
d. Common reasons for study discontinuation in the intervention vs. control arm were: withdrawal of consent (7% vs. 7%), patient decision (5% vs. 4%), AE (4% vs. 2%). In addition, one patient in each the intervention and the control arm died under treatment with the study medication.

AChEI: acetylcholinesterase inhibitors; ADAS-Cog 14: Alzheimer's Disease Assessment Scale – Cognitive subscale (14-item version); ApoE ε4: apolipoprotein E ε4; CDR: Clinical Dementia Rating; CDR-GS: Clinical Dementia Rating-Global Score; CDR-SB: Clinical Dementia Rating-Sum of Boxes; f: female; IxRS: interactive voice/web response system; m: male; MMST: Mini Mental State Examination; n: number of patients in the category; N: number of analysed patients; ND: no data; QOL-AD: Quality of Life in Alzheimer's Disease Scale; RCT: randomized controlled trial; SD: standard deviation

The mean age of the patients was around 72 or 69 years; most of them were of European or North American family origin. The proportion of men and women was balanced. On average, the first symptoms appeared in patients four years prior to study inclusion.

At the start of the study, the patients had a CDR-SB (scale from 0 to 18) of 3.7. At baseline, the scores on the ADAS-Cog14 assessment scale for Alzheimer's disease were 27 each, on a scale ranging from 0 to 90, with higher scores indicating more severe cognitive impairment. The QOL-AD scores for the recording of the quality of life in individuals with Alzheimer's disease (scale from 13 to 52) averaged 39 and 38 respectively, with higher scores indicating a better quality of life. No data on CDR-GS or MMST at baseline are available for the populations described, although these were defined as inclusion criteria for the study.

Over the course of the study, more patients in the intervention arm discontinued treatment prematurely than in the control arm (21% vs. 17%). Common reasons for treatment discontinuation were withdrawal of consent, AEs and patient decision. The majority of patients who discontinued treatment also discontinued the study (21% vs. 16%).

Overall, the demographic and clinical characteristics of the patients included are considered to be sufficiently comparable.

Concomitant treatments

The data on concomitant treatments at baseline and in the course of the study are presented in Table 12.

Table 12: Concomitant medication at baseline and in the course of the study – RCT, direct comparison: lecanemab + AChEI versus placebo + AChEI (research question 2)

Study	Patients with anti-dementia treatment, n (%)	
	lecanemab	placebo
CLARITY AD	N[a] = 136	N[a] = 137
Concomitant anti-dementia medication during the study	136 (100)	137 (100)
Stable medication	124 (91)	115 (84)
Changes to medication during the study	12 (9)	22 (16)
New medication	5 (4)	6 (4)
Dose increase	6 (4)	13 (10)
Dose reduction	3 (2)	8 (6)
Discontinuation of medication	4 (3)	11 (8)
Anti-dementia drugs at baseline and during the study[b]	136 (100)	137 (100)
Donepezil	111 (82)	99 (72)
Galantamine	8 (6)	14 (10)
Memantine	4 (3)	1 (1)
Rivastigmine	18 (13)	31 (23)

a. ITT-FAS+: patients who received at least one dose of the respective treatment and for whom a baseline value and at least one post-baseline questionnaire evaluation in the CDR were available.
b. Patients were able to take several drugs.

AChEI: acetylcholinesterase inhibitors; CDR: Clinical Dementia Rating; n: number of patients in the category; N: number of analysed patients; RCT: randomized controlled trial

During the course of the study, concomitant treatments were adjusted in 9% and 16% of patients respectively, with the majority of patients in both arms receiving treatment with donepezil in the course of the study. A small proportion of patients began treatment with memantine, which is only approved for use from the stage of moderate dementia onwards. As no reasons have been given, it remains unclear whether the change in treatment was associated with disease progression. However, the proportion of patients affected is considered to be negligible.

Overall, the concomitant medication was sufficiently comparable in both study arms. However, details regarding the dosage and the reasons for adjusting the treatment are still missing. Information on non-drug treatments is also still lacking.

Treatment duration and observation period

Table 13 shows the mean and median treatment duration of the patients as well as the mean and median observation period for individual outcomes.

Table 13: Information on the course of the study – RCT, direct comparison: lecanemab + AChEI versus placebo + AChEI (research question 2)

Study	**CLARITY AD**	
duration of the study phase **outcome category/outcome**	**lecanemab**	**placebo**
Treatment duration [months]	N = 139	N = 138
Median [min; max]	18.0 [0.5; 18.8]	18.0 [4.0; 18.7]
Mean (SD)	15.5 (5.0)	16.8 (3.2)
Observation period [months]		
All-cause mortality[a, b]	N = 139	N = 138
Median [Q1; Q3]	17.0 [16.2; 17.2]	17.0 [16.9; 17.1]
Mean (SD)	14.8 (4.6)	16 (2.9)
Morbidity	N = 136	N = 137
Symptoms (CDR-SB)[c]		
Median [Q1; Q3]	18.0 [17.3; 18.2]	18.0 [17.8; 18.1]
Mean (SD)	15.7 (4.9)	16.6 (3.6)
Cognition (ADAS-Cog14)c		
Median [Q1; Q3]	18.0 [15.1; 18.2]	18.0 [17.7; 18.1]
Mean (SD)	15.4 (5.1)	16.5 (3.7)
Health status (EQ-5D VAS)c		
Median [Q1; Q3]	18.0 [17.1; 18.2]	18.0 [17.8; 18.1]
Mean (SD)	15.2 (5.7)	16.1 (4.6)
Health-related quality of life (QOL-AD)c	N = 136	N = 137
Median [Q1; Q3]	18.0 [17.3; 18.2]	18.0 [17.8; 18.1]
Mean (SD)	15.2 (5.7)	16.1 (4.6)
Side effects[b]	N = 139	N = 138
Median [Q1; Q3]	17.0 [16.2; 17.2]	17.0 [16.9; 17.1]
Mean (SD)	14.8 (4.6)	16 (2.9)

a. All-cause mortality was recorded as fatal adverse event.
b. According to the company, AEs were defined as any event occurring during treatment or within 30 days of the last dose of the study medication.
c. The observation period is defined as the time from randomization to the last recording with the respectIve instrument (without follow-up visit).

AChEI: acetylcholinesterase inhibitor; ADAS-Cog 14: Alzheimer's Disease Assessment Scale – Cognitive subscale (14-item version); CDR-SB: Clinical Dementia Rating-Sum of Boxes; max: maximum; min: minimum; N: number of analysed patients;: Q1: 1st quartile; Q3: 3rd quartile; QOL-AD: Quality of Life in Alzheimer's Disease Scale; RCT: randomized controlled trial; SD: standard deviation; VAS: visual analogue scale

During the RCT phase of the CLARITY AD study, the mean treatment duration of patients in the intervention and the control arm was 16 and 17 months respectively. The observation period for the outcomes of the categories morbidity and health-related quality of life differed between the study arms. In the intervention and the control arm, the duration was 16 and 17

months respectively for the outcome symptoms (CDR-SB), and 15 and 17 months for the outcome cognition (ADAS-Cog14), 15 and 17 months respectively, and for the outcomes health status (EQ-5D VAS) and health-related quality of life (QOL-AD) it was 15 and 16 months respectively. The outcomes of the side effects category and all-cause mortality were observed for an average of 15 and 16 months, respectively, during the RCT phase.

Overall, treatment duration and observation periods are considered to be sufficiently comparable between the study arms.

2.2.2 Results on added benefit

2.2.2.1 Outcomes included

The outcomes used for the benefit assessment are described in dossier assessment A25-111 [1].

Table 14 shows for which outcomes data were available in the included study.

Table 14: Matrix of outcomes – RCT, direct comparison: lecanemab + AChEI versus placebo + AChEI (research question 2)

Study	Outcomes											
	All-cause mortality[a]	Symptoms (CDR-SB)	Cognition (ADAS-Cog14)	Independence in everyday life	Behavioural changes	Health status (EQ-5D VAS)	Health-related quality of life (QOL AD)	SAEs	Discontinuation due to AEs	Symptomatic ARIA events[b]	Infusion related reactionc (AEs)	Urinary tract infections (PT, AEs)
CLARITY AD	Yes	Yes	Yes	No[d]	No[d]	Yes	Yes	Yes	Yes	Yes	Yes	Yes

a. The results on all-cause mortality are based on the information on fatal AEs.
b. The following events are considered: symptomatic ARIA-E, symptomatic ARIA-H, serious ARIA-E and serious ARIA-H.
c. Operationalized via a PT list compiled by the company; for further details, see dossier assessment A25-111, Section I 4.2.1 [1].
d. No suitable data available; for justification see dossier assessment A25-111, Section I 4.2.1 [1].

AAChEI: acetylcholinesterase inhibitors; ADAS-Cog 14: Alzheimer's Disease Assessment Scale – Cognitive Subscale, 14-item version; AE: adverse event; ARIA-E: amyloid-related imaging abnormalities-oedema/effusion; ARIA-H: amyloid-related imaging abnormalities – haemorrhage; CDR-SB: Clinical Dementia Rating-Sum of Boxes; PT: Preferred Term; QOL-AD: Quality of Life in Alzheimer's Disease Scale; RCT: randomized controlled trial; SAE: serious adverse event; VAS: visual analogue scale

2.2.2.2 Risk of bias and certainty of conclusions

In dossier assessment A25-111 [1], the risk of bias across outcomes was rated as low.

Table 15 shows the risk of bias for CLARITY AD at outcome level.

Table 15: Risk of bias across outcomes and outcome-specific risk of bias – RCT, direct comparison: lecanemab + AChEI versus placebo + AChEI (research question 2)

Study		Outcomes											
	Study level	All-cause mortality[a]	Symptoms (CDR-SB)	Cognition (ADAS-Cog14)	Independence in everyday life	Behavioural changes	Health status (EQ-5D VAS)	Health-related quality of life (QOL AD)	SAEs	Discontinuation due to AEs	Symptomatic ARIA events[b]	Infusion related reaction[c] (AEs)	Urinary tract infections (PT, AEs)
CLARITY AD	N	H[d]	H[e]	H[e]	–[f]	–[f]	H[e]	H[e]	H[d]	L[g]	H[d]	H[d]	H[d]

a. The results on all-cause mortality are based on the information on fatal AEs.
b. The following events are considered: symptomatic ARIA-E, symptomatic ARIA-H, serious ARIA-E and serious ARIA-H.
c. Operationalized via a PT list compiled by the company; for further details, see dossier assessment A25-111, Section I 4.2.1 [1].
d. Incomplete observations for potentially informative reasons.
e. High proportion of patients not included in the analysis (> 10%) and large difference between the treatment groups (> 5 percentage points).
f. No suitable data available; for justification see dossier assessment A25-111, Section I 3. [1].
g. Despite the low risk of bias, the certainty of results is presumably limited for the outcome of discontinuation due to AEs.

AAChEI: acetylcholinesterase inhibitors; ADAS-Cog 14: Alzheimer's Disease Assessment Scale – Cognitive Subscale, 14-item version; ARIA-E: amyloid-related imaging abnormalities-oedema/effusion; ARIA-H: amyloid-related imaging abnormalities – haemorrhage; CDR-SB: Clinical Dementia Rating-Sum of Boxes; H: high; L: low; PT: Preferred Term; QOL-AD: Quality of Life in Alzheimer's Disease Scale; RCT: randomized controlled trial; SAE: serious adverse event; VAS: visual analogue scale

As part of the commenting procedure, the company submitted new data on the study course and on treatment and study discontinuations. The risk of bias of the subsequently submitted results for the specific AE outcomes symptomatic ARIA events and urinary tract infections (AE) as well as for the other side effects and all-cause mortality was rated as high due to incomplete observations for potentially informative reasons. For all outcomes in the categories morbidity and health-related quality of life, the company provided information on response rates in its comments. The data presented show a high proportion of patients not included in the analysis

(> 10%) and a large difference of the response rates between the treatment groups (> 5 percentage points). The assessment of the risk of bias for the outcomes in the categories morbidity and health-related quality of life described in dossier assessment A25-111 therefore remains unchanged. The risk of bias is still rated as high for these outcomes.

Dossier assessment A25-111 described further aspects that led to a reduction in the certainty of conclusions: a lack of information on the use of the AChEI, a lack of guidelines on how to deal with a lack of efficacy or progression to the next stage, as well as a lack of data on non-drug therapies. In its comments, the company has not provided the data required to assess these further aspects. The certainty of conclusions therefore remains restricted. At most hints, e.g. of an added benefit, can be derived.

2.2.2.3 Results

Table 16 and Table 17 summarizes the results from the comparison of lecanemab + AChEI with placebo + AChEI in patients with mild Alzheimer's dementia with AChEI at baseline who are ApoE ε4 non-carriers or heterozygotes, and who were not using any anticoagulants at baseline. Unlike in the dossier assessment, stratified analyses are now available for the outcomes of the categories morbidity and health-related quality of life. Where necessary, calculations conducted by the Institute are provided in addition to the data from the company's comments.

Tables on common AEs, common SAEs and discontinuations due to AEs are presented in Appendix E.2.

Further details on symptomatic ARIA events are set out in Appendix D.

Table 16: Results (mortality, morbidity, health-related quality of life, side effects, dichotomous) – RCT, direct comparison: lecanemab + AChEI versus placebo + AChEI (research question 2) (multipage table)

Study outcome category outcome	Lecanemab + AChEI N	 patients with event n (%)	Placebo + AChEI N	 patients with event n (%)	Lecanemab vs. placebo RR [95% CI]; p-value
CLARITY AD					
Mortality					
All-cause mortality[a]	139	1 (0.7)	138	1 (0.7)	0.99 [0.06; 15.71]; > 0.999[b]
Morbidity					
Symptoms (CDR-SB – deterioration at Month 18[c])	103	28 (27.2)	115	39 (33.9)	0.84 [0.56; 1.27]; 0.410[d]
Cognition (ADAS-Cog14 – deterioration at Month 18[e])	99	14 (14.1)	111	26 (23.4)	0.63 [0.35; 1.14]; 0.130[d]
Independence in everyday life			No suitable data[f]		
Behavioural changes			No suitable data[f]		
Health status (EQ-5D VAS – deterioration at Month 18[g])	103	16 (15.5)	113	25 (22.1)	0.66 [0.38; 1.17]; 0.155[d]
Health-related quality of life					
QOL-AD – deterioration at Month 18[h])	104	10 (9.6)	113	19 (16.8)	0.56 [0.28; 1.15]; 0.115[d]
Side effects					
AEs (supplementary information)o	139	127 (91.4)	138	111 (80.4)	–
SAEs[i]	139	20 (14.4)	138	14 (10.1)	1.42 [0.75; 2.70]; 0.293[b]
Discontinuation due to AEs	139	10 (7.2)	138	4 (2.9)	2.48 [0.80; 7.73]; 0.126[b]
Symptomatic ARIA events[j]	139	7 (5.0)	138	1 (0.7)	6.95 [0.87; 55.74]; 0.034[b]
Infusion related reaction (AE)k	139	32 (23.0)	138	10 (7.2)	3.18 [1.63; 6.21]; < 0.001[b]
Urinary tract infections (PT, AEs)	139	5 (3.6)	138	17 (12.3)	0.29 [0.11; 0.77]; 0.008[b]

Table 16: Results (mortality, morbidity, health-related quality of life, side effects, dichotomous) – RCT, direct comparison: lecanemab + AChEI versus placebo + AChEI (research question 2) (multipage table)

Study outcome category outcome	Lecanemab + AChEI N patients with event n (%)	Placebo + AChEI N patients with event n (%)	Lecanemab vs. placebo RR [95% CI]; p-value
a. The results on all-cause mortality are based on the information on fatal AEs. b. Effect and CI: unstratified logistic regression model; p-value: Institute's calculation (unconditional exact test [CSZ method according to [6]]). c. An increase of the CDR-SB by ≥ 2.7 points (15% of the scale range) from baseline is considered a clinically relevant deterioration (score range of the scale: 0 to 18). d. Effect, CI and p-value: logistic regression model stratified by treatment, subpopulation, AChEI use at baseline, ApoE-ε4 status and region. e. An increase by ≥ 13.5 points (15% of the scale range) from baseline is considered a clinically relevant deterioration (score range of the scale 0 to 90). f. For justification see Section I 4.2.1 of dossier assessment A25-111 [1]. g. A decrease by ≥ 15 points (15% of the scale range) from baseline is considered a clinically relevant deterioration (score range of the scale: 0 to 100). h. A decrease by ≥ 5.85 points (15% of the scale range) from baseline is considered a clinically relevant deterioration (score range of the scale 13 and 52). i. With the exclusion of disease-related events (see Section I 4.2.1 of dossier assessment A25-111 [1]). j. The following events are considered: symptomatic ARIA-E, symptomatic ARIA-H, serious ARIA-E and serious ARIA-H (see also Table 25 in Appendix D assessment). k. Operationalized via a PT list compiled by the company (see dossier assessment A25-111, Section I 4.2.1 [1]). AChEI: acetylcholinesterase inhibitors; ADAS-Cog 14: Alzheimer's Disease Assessment Scale – Cognitive Subscale, 14-item version; AE: adverse event; ARIA: amyloid-related imaging abnormalities; ARIA-E: amyloid-related imaging abnormalities-oedema/effusion; ARIA-H: amyloid-related imaging abnormalities – haemorrhage; CDR-SB: Clinical Dementia Rating-Sum of Boxes; CI: confidence interval; n: number of patients with (at least one) event; N: number of analysed patients; QOL-AD: Quality of life in Alzheimer's Disease Scale; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; VAS: visual analogue scale			

Table 17: Results (morbidity, continuous - supplementary presentation) – RCT, direct comparison: lecanemab ± AChEI vs. placebo ± AChEI (research question 2)

Study outcome category	Lecanemab ± AChEI			Placebo ± AChEI			Lecanemab ± AChEI vs. placebo ± AChEI
outcome	N[a]	values at baseline mean (SD)	change at month 18 mean[b] (SE)	N[a]	values at baseline mean (SD)	change at month 18 mean[b] (SE)	mean difference [95% CI][b]; p-value
CLARITY AD							
Morbidity							
Symptoms (CDR-SB)[c]	136	3.7 (1.29)	1.87 (0.24)	137	3.7 (1.38)	2.61 (0.23)	−0.74 [−1.40; −0.09] 0.026 SMD: −0.30 [−0.57; −0.03][d]
Cognition (ADAS Cog14)[e]	136	27.3 (6.9)	7.17 (1.04)	137	27.0 (7.9)	10.08 (0.99)	−2.91 [−5.71; −0.10]; 0.042 SMD: −0.28 [−0.55; −0.01][d]
Health status (EQ-5D VAS)[f]	126	83.9 (11.9)	−2.43 (1.5)	132	80.0 (15.0)	-5.03 (1.41)	2.61 [−1.37; 6.58]; 0.198
Health-related quality of life							
QOL-AD[g]	126	39.3 (6.1)	−0.21 (0.53)	132	38.3 (6.5)	−2.25 (0.51)	2.04 [0.61; 3.47]; 0.005 SMD: 0.38 [0.11; 0.64][d]

a. Number of patients considered in the effect estimation.
b. MMRM analysis with treatment group, region, visit, subpopulation, ApoE-ε4 status, AChEI use at baseline, baseline value, interactions treatment group*visit and baseline value*visit.
c. Lower (decreasing) values indicate improved symptoms; negative effects (intervention minus comparison) indicate an advantage of the intervention (scale range: 0 to 18).
d. The SMD was considered to check the relevance of the result. The 95% CI of the SMD was not fully below the irrelevance threshold of −0.2. It can therefore not be inferred that the effect is relevant.
e. Lower (decreasing) values indicate improved symptoms; negative effects (intervention minus comparison) indicate an advantage of the intervention (scale range: 0 to 90).
f. Higher (increasing) values indicate better health status; positive effects (intervention minus comparison) indicate an advantage for the intervention (scale range: 0 to 100).
g. Higher (increasing) values indicate better health-related quality of life; positive effects (intervention minus comparison) indicate an advantage for the intervention (scale range: 13 to 52).

AChEI: acetylcholinesterase inhibitors; ADAS-Cog 14: Alzheimer's Disease Assessment Scale – Cognitive Subscale, 14-item version; CDR-SB: Clinical Dementia Rating-Sum of Boxes; CI: confidence interval; MMRM: mixed-effects model with repeated measures; N: number of analysed patients; QOL-AD: Quality of Life in Alzheimer's Disease Scale; RCT: randomized controlled trial; SD: standard deviation; SE: standard error; SMD: standardized mean difference

Based on the available information, at most hints, e.g. of an added benefit, can be determined for all data subsequently submitted with the comments (see Section 2.2.2.2 of this addendum for reasoning).

Mortality

All-cause mortality

No statistically significant difference between treatment groups was found for the outcome of all-cause mortality. There was no hint of an added benefit of lecanemab + AChEI in comparison with AChEI; an added benefit is therefore not proven.

Morbidity

Symptoms (CDR-SB)

No statistically significant difference between treatment groups was found for the outcome of symptoms (recorded using the CDR-SB). There was no hint of an added benefit of lecanemab + AChEI in comparison with AChEI; an added benefit is therefore not proven.

The continuous analyses presented as supplementary information show a statistically significant difference between the treatment groups, which, however, turns out to be irrelevant when considering the SMD, as the 95% CI of the effect does not lie entirely outside the irrelevance threshold of [−0.2; 0.2].

Cognition (ADAS-Cog14)

No statistically significant difference between treatment groups was found for the outcome cognition, recorded using the ADAS-Cog14). There was no hint of an added benefit of lecanemab + AChEI in comparison with AChEI; an added benefit is therefore not proven.

The continuous analyses presented as supplementary information show a statistically significant difference between the treatment groups, which, however, turns out to be irrelevant when considering the SMD, as the 95% CI of the effect does not lie entirely outside the irrelevance threshold of [−0.2; 0.2].

Independence in everyday life

No suitable data were available for the outcome independence in everyday life (see Section I 4.2.1 of dossier assessment A25-111 for reasoning). There was no hint of an added benefit of lecanemab + AChEI in comparison with AChEI; an added benefit is therefore not proven.

Behavioural changes

No suitable data were available for the outcome behavioural changes (see Section I 4.2.1 of dossier assessment A25-111 for reasoning). There was no hint of an added benefit of lecanemab + AChEI in comparison with AChEI; an added benefit is therefore not proven.

Health status (EQ-5D VAS)

For the outcome of health status, recorded using the EQ-5D VAS, no statistically significant difference was found between treatment groups. There was no hint of an added benefit of lecanemab + AChEI in comparison with AChEI; an added benefit is therefore not proven.

The continuous analyses presented as supplementary information also show no statistically significant difference between treatment groups.

Health-related quality of life (QOL AD)

No statistically significant difference between treatment groups was found for the outcome health-related quality of life, recorded using the QOL-AD. There was no hint of an added benefit of lecanemab + AChEI in comparison with AChEI; an added benefit is therefore not proven.

The continuous analyses presented as supplementary information show a statistically significant difference between the treatment groups, which, however, turns out to be irrelevant when considering the SMD, as the 95% CI of the effect does not lie entirely outside the irrelevance threshold of [−0.2; 0.2].

Side effects

SAEs and discontinuation due to AEs

No statistically significant difference between treatment groups was found for either of the outcomes SAEs or discontinuation due to AEs. In each case, there was no hint of greater or lesser harm from lecanemab + AChEI in comparison with AChEI for either of them; greater or lesser harm is therefore not proven.

Symptomatic ARIA events

A statistically significant difference to the disadvantage of lecanemab + AChEI compared with AChEI was shown for the outcome symptomatic ARIA events. There is a discrepancy between the CI and the p-value. The difference is therefore no more than marginal for this outcome in the category non-serious/non-severe side effects in the subpopulation under consideration (see also Section 2.2.3.1). There was no hint of greater or lesser harm from lecanemab + AChEI in comparison with AChEI; greater or lesser harm is therefore not proven.

Infusion related reaction (AEs)

A statistically significant difference to the disadvantage of lecanemab + AChEI compared with AChEI was shown for the outcome infusion-related reactions (AEs). There was a hint of greater harm from lecanemab + AChEI in comparison with AChEI.

Urinary tract infections (AEs)

For the outcome urinary tract infections (AEs), a statistically significant difference was shown in favour of lecanemab + AChEI compared with AChEI. There was a hint of lesser harm from lecanemab + AChEI in comparison with AChEI.

2.2.2.4 Subgroups and other effect modifiers

The following potential effect modifiers were considered for the present benefit assessment:

- Sex (male versus female)
- Age (< 65 years versus ≥ 65 and < 75 years versus ≥ 75 years)

Subgroup analyses of the 2 characteristics mentioned were planned a priori.

Interaction tests are performed when at least 10 patients per subgroup are included in the analysis. For binary data, there must also be at least 10 events in at least one subgroup.

Only the results with an effect modification with a statistically significant interaction between treatment and subgroup characteristic (p-value < 0.05) are presented. In addition, subgroup results are only presented if there is a statistically significant and relevant effect in at least one subgroup.

Using the methods described above, the available subgroup analyses did not reveal any effect modifications.

2.2.3 Probability and extent of added benefit

The probability and extent of added benefit at outcome level are derived below, taking into account the different outcome categories and effect sizes. The methods used for this purpose are explained in the *General Methods* of IQWiG [7].

The approach for deriving an overall conclusion on the added benefit based on the aggregation of conclusions derived at outcome level is a proposal by IQWiG. The G-BA decides on the added benefit.

2.2.3.1 Assessment of added benefit at outcome level

The extent of the respective added benefit at outcome level was assessed based on the results presented in Section 2.2.2.3 (see Table 18).

Determination of the outcome category for the outcome symptomatic ARIA events

The following events are considered for the outcome symptomatic ARIA events: symptomatic ARIA-E, symptomatic ARIA-H, serious ARIA-E and serious ARIA-H. The data subsequently submitted as part of the commenting procedure show that the outcome predominantly

includes non-serious ARIA. Therefore, the outcome was assigned to the outcome category non-serious/non-severe side effects.

Table 18: Extent of added benefit at outcome level: lecanemab + AChEI versus AChEI (research question 2) (multipage table)

Outcome category **outcome**	**Lecanemab + AChEI vs. AChEI** **proportion of events (%)** **effect estimation [95% CI];** **p-value** **probability**[a]	**Derivation of extent**[b]
Mortality		
All-cause mortality	0.7% vs. 0.7% RR: 0.99 [0.06; 15.71]; p > 0.999	Lesser benefit not proven/added benefit not proven
Morbidity		
Symptoms (CDR-SB – deterioration at Month 18)	27.2% vs. 33.9% RR: 0.84 [0.56; 1.27]; p = 0.410	Lesser benefit not proven/added benefit not proven
Cognition (ADAS-Cog14 – deterioration at Month 18)	14.1% vs. 23.4% RR: 0.63 [0.35; 1.14]; p = 0.130	Lesser benefit not proven/added benefit not proven
Independence in everyday life	No suitable data	Lesser benefit not proven/added benefit not proven
Behavioural changes	No suitable data	Lesser benefit not proven/added benefit not proven
Health status (EQ-5D VAS – deterioration at Month 18)	15.5% vs. 22.1% RR: 0.66 [0.38; 1.17]; p = 0.155	Lesser benefit not proven/added benefit not proven
Health-related quality of life		
QOL-AD (deterioration at Month 18)	9.6% vs. 16.8% RR: 0.56 [0.28; 1.15]; p = 0.115	Lesser benefit not proven/added benefit not proven
Side effects		
SAEs	14.4% vs. 10.1% RR: 1.42 [0.75; 2.69]; p = 0.293	Greater/lesser harm not proven
Discontinuation due to AEs	7.2% vs. 2.9% RR: 2.48 [0.80; 7.73]; p = 0.126	Greater/lesser harm not proven
Symptomatic ARIA events	5.0% vs. 0.7% RR: 6.95 [0.87; 55.74] RR: 0.14 [0.02; 1.15][c]; p = 0.034	Outcome category: non-serious/non-severe symptoms/late complications $1 < CI_u$, $p < 0.05$ lesser benefit/added benefit not provend

Table 18: Extent of added benefit at outcome level: lecanemab + AChEI versus AChEI (research question 2) (multipage table)

Outcome category **outcome**	**Lecanemab + AChEI vs. AChEI** **proportion of events (%)** **effect estimation [95% CI];** **p-value** **probability**[a]	**Derivation of extent**[b]
Infusion-related reaction (AE)	23.0% vs. 7.2% RR: 3.18 [1.63; 6.21] RR: 0.31 [0.16; 0.61][c]; p < 0.001 probability: hint	Outcome category: non-serious/non-severe side effects CI_u < 0.80 greater harm, extent: considerable
Urinary tract infection (AE)	3.6% vs. 12.3% RR: 0.29 [0.11; 0.77]; p = 0.008 probability: hint	Outcome category: non-serious/non-severe side effects CI_u < 0.80 lesser harm, extent: considerable

a. Probability provided if there is a statistically significant and relevant effect.
b. Depending on the outcome category, the effect size is estimated using different limits based on the upper limit of the confidence interval (CI_u).
c. Institute's calculation; inverse direction of effect to enable use of limits to derive the extent of the added benefit.
d. Discrepancy between CI and p-value. The result of the statistical test (p-value) is decisive for the derivation of the added benefit. The extent of the effect in this non-serious/non-severe outcome was no more than marginal.

AChEI: acetylcholinesterase inhibitors; ADAS-Cog 14: Alzheimer's Disease Assessment Scale – Cognitive Subscale, 14-item version; AE: adverse event; ARIA: amyloid-related imaging abnormalities; CDR-SB: Clinical Dementia Rating – Sum of Boxes; CI: confidence interval; CI_u: upper limit of the confidence interval; ND: no data; QOL-AD: Quality of life in Alzheimer's Disease Scale; SAE: serious adverse event; VAS: visual analogue scale

2.2.3.2 Overall conclusion on added benefit

Table 19 summarizes the results taken into account for the overall conclusion on the extent of the added benefit.

Table 19: Positive and negative effects from the assessment of lecanemab + AChEI in comparison with AChEI (research question 2)

Positive effects	**Negative effects**
Non-serious/non-severe side effects ▪ urinary tract infection (AE): hint of lesser harm – extent: "considerable"	Non-serious/non-severe side effects ▪ infusion related reaction (AE): hint of greater harm – extent "considerable"
No suitable data are available for the outcomes independence in everyday life and behavioural changes.	
AChEI: acetylcholinesterase inhibitors; AE: adverse event	

Taking into account the analyses subsequently submitted with the commenting procedure, the overall consideration shows both a positive and a negative effect of lecanemab compared with the ACT for research question 2. The positive effect with considerable extent in the category non-serious/non-severe side effects based on a specific AE (urinary tract infections) is offset by a negative effect with considerable extent in the category non-serious/non-severe side effects based on a specific AE (infusion-related reactions).

For symptomatic ARIA events there is a CI covering the zero effect, meaning that no relevant effect was observed in the relevant subpopulation (see also Figure 22). No relevant effect modification was shown in the subgroup characteristics age and sex.

Contextualisation of the overall conclusion before the background of the commenting procedure

With regard to the criticism expressed during the commenting procedure concerning the use of the 15% criterion in this therapeutic indication, it should be emphasized that the continuous analyses presented as supplementary information show statistically significant differences between the treatment groups in a few outcomes, which, however, turn out to be irrelevant when considering the SMD, as the 95% CI of the effect does not lie entirely outside the irrelevance threshold of [−0.2; 0.2].

With regard to the criticism expressed during the commenting procedure concerning the consideration of the subpopulations in accordance with the G-BA's research questions, it should be emphasized that, unlike for the MCI (see Section 2.1.3.2), the overall consideration of the forest plots of the various mild Alzheimer's dementia populations reveals no clear pattern across the outcomes of the categories morbidity and health-related quality of life. Related to patients with mild Alzheimer's dementia who did not receive AChEIs in the CLARITY AD study, it remains unclear whether this was for a valid reason or simply due to availability. The company did not present any clarifying information with the commenting procedure.

Irrespective of this, it should be noted that with regard to the significant positive effects of lecanemab in the approval population, significant effects in favour of lecanemab were observed only in the CDR-SB and the ADAS-Cog14 (based on the stratified evaluations in the responder analyses); these (depending on the determination of an outcome category) would, at most, be classified as minor or mild and would need to be weighed against several relevant side effects (see below). It should also be emphasized that the continuous analyses for the CDR-SB show a significant but, when considering the SMD, non-relevant difference also in the approval population, as the 95% CI of the effect is not entirely outside the irrelevance threshold of [−0.2; 0.2] (see also Figure 9 and Figure 16).

The forest plots on side effects (see Figure 20 to Figure 23 in Appendix C) show that the effect estimates for the various populations largely lie one below the other, and that only the width

of the CI changes when subpopulations are considered. Therefore, comparable disadvantages can be assumed in terms of side effects in the relevant subpopulations compared with the approval population, particularly in the case of symptomatic ARIA. In the approval population or the pooled population from research questions 1 and 2, there is a relevant extent of disadvantages for other outcomes on side effects in addition to infusion-related reactions (symptomatic ARIA and/or discontinuation due to AEs).

With regard to the data from the open-label extension phase of the CLARITY AD study discussed at the oral hearing, it should be noted that the company has still not submitted these data in a form compliant with the dossier template also within the framework of the commenting procedure, meaning that they cannot be assessed due to missing information.

Summary

In summary, the available data yield no hint of an added benefit of lecanemab (as add-on therapy to ongoing AChEI therapy) for patients with clinically diagnosed mild Alzheimer's dementia, who are ApoE ε4-non carriers or heterozygotes. An added benefit is therefore not proven.

2.3 Summary

The data subsequently submitted by the company in the commenting procedure and following the oral hearing do not change the conclusion regarding the added benefit of lecanemab set out in dossier assessment A25-111.

The following Table 20 shows the result of the benefit assessment of lecanemab, taking into account dossier assessment A25-111 and this addendum.

Table 20: Lecanemab – probability and extent of added benefit

Research question	Therapeutic indication	ACT[a]	Probability and extent of added benefit
Adults with early Alzheimer's disease who are apolipoprotein E ε4 (ApoE ε4) non-carriers or heterozygotes with confirmed amyloid pathology:			
1	With clinically diagnosed MCI due to Alzheimer's disease	Watchful waiting[b]	Added benefit not proven (based on the results of the relevant study)
2	With a clinical diagnosis of mild dementia due to Alzheimer's disease	Donepezil or galantamine or rivastigmine[b, c]	▪ lecanemab as add-on therapy to existing AChEI treatment: added benefit not proven (based on the results of the relevant study[d]) ▪ lecanemab monotherapy: added benefit not proven (no relevant study[e])

a. Presentation of the respective ACT specified by the G-BA.
b. Non-drug measures as defined in the German Remedies Directive or the Medicines Catalogue (occupational therapy, e.g. cognitive training) should, where appropriate, be offered in both study arms. The type and scope of the interventions used must be documented.
c. Acetylcholinesterase inhibitors (AChEIs) (donepezil, galantamine and rivastigmine) are approved for the symptomatic treatment of mild to moderate Alzheimer's dementia. The aim should be to administer the highest tolerable dose. For the benefit assessment, the on-label use of drugs within the context of a study must be observed.
d. The CLARITY AD study only included patients (with regard to the pretreated patient group relevant to research question 2) who had been receiving stable AChEI therapy for at least 12 weeks. It remains unclear whether the observed effects are transferable to patients without existing or with unstable AChEI therapy.
e. The research question of lecanemab as monotherapy compared with treatment with donepezil, galantamine or rivastigmine was not investigated in the CLARITY AD study.

AChEI: acetylcholinesterase inhibitors; ApoE ε4: apolipoprotein E ε4; GBA: Federal Joint Committee; MCI: mild cognitive impairment

The G-BA decides on the added benefit.

3 References

The reference list contains citations provided by the company in which bibliographical information may be missing.

1. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Lecanemab (frühe Alzheimer-Krankheit); Nutzenbewertung gemäß § 35a SGB V; Dossierbewertung [online]. 2025 [Accessed: 01.12.2025]. URL: https://doi.org/10.60584/A25-111.

2. Eisai. Zusatzanalysen zur schriftlichen Stellungnahme von Lecanemab für die Gesamtpopulation, EU-Gesamtpopulation und EU-Teilpopulation gemäß G-BA-ZVT der Studie Clarity AD [unpublished].

3. Eisai. Anhang 2: Zusatzanalysen der Zeit bis zur Verschlechterung im CDR-SB-Gesamtscore und im globalen CDR-Score zum Nutzenbewertungsverfahren von Lecanemab für die EU-Gesamtpopulation, EU-Teilpopulation leichte Demenz ohne Memantin und EU-Teilpopulation gemäß G-BA-ZVT der Studie Clarity AD [unpublished].

4. Eisai. Lecanemab (LEQEMBI); Dossier zur Nutzenbewertung gemäß § 35a SGB V [online]. 2025 [Accessed: 10.12.2025]. URL: https://www.g-ba.de/bewertungsverfahren/nutzenbewertung/1257/#dossier.

5. Gemeinsamer Bundesausschuss. Mündliche Anhörung gemäß § 35a Absatz 3 Satz 2 SGB V des Gemeinsamen Bundesausschusses; hier: Lecanemab (D-1054); Stenografisches Wortprotokoll [online]. 2026 [Accessed: 28.01.2026]. URL: https://www.g-ba.de/downloads/91-1031-1257/2025-01-12_Wortprotokoll_Lecanemab_D-1054.pdf.

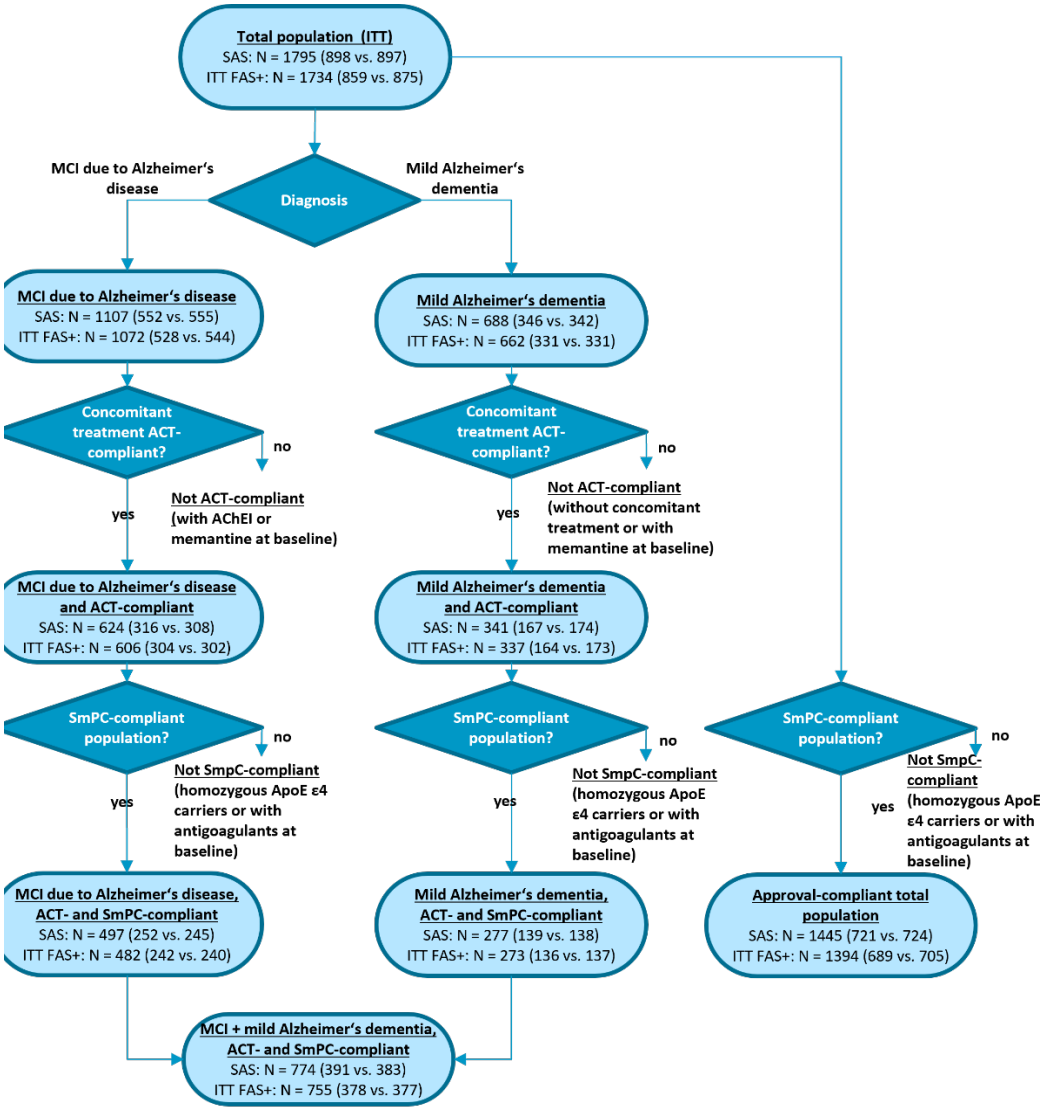
6. Martín Andrés A, Silva Mato A. Choosing the optimal unconditioned test for comparing two independent proportions. Computat Stat Data Anal 1994; 17(5): 555-574. https://doi.org/10.1016/0167-9473(94)90148-1.

7. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Allgemeine Methoden; Version 8.0 [online]. 2025 [Accessed: 07.01.2026]. URL: https://doi.org/10.60584/Allgemeine-Methoden_V8.0.

8. National Institute for Health and Care Excellence. Lecanemab for treating mild cognitive impairment or mild dementia caused by Alzheimer's disease; Final draft guidance [online]. 2025 [Accessed: 26.01.2026]. URL: https://www.nice.org.uk/guidance/gid-ta11220/documents/674.

9. National Institute for Health and Care Excellence. Single Technology Appraisal; Lecanemab for treating mild cognitive impairment or mild dementia caused by Alzheimer's disease [ID4043]; Committee Papers [online]. 2024 [Accessed: 26.01.2026]. URL: https://www.nice.org.uk/guidance/gid-ta11220/documents/committee-papers.

Appendix A Flowchart on the formation of the subpopulations



ACT: appropriate comparator therapy; ApoE ε4: apolipoprotein E ε4; ITT FAS+: patients who received at least one dose of the respective treatment and for whom a baseline value and at least one post-baseline questionnaire evaluation within the Clinical Dementia Rating were available; MCI: mild cognitive impairment; N: number of patients; SAS: patients who received at least one dose of the respective treatment; SmPC: Summary of Product Characteristics

Figure 2: Flowchart showing the formation of subpopulations from the total population of the CLARITY AD study

Appendix B Supplementary analyses and informative graphs on the CDR-SB and its domains for the relevant subpopulations

B.1 Supplementary presentation of results for the CDR-SB for the relevant subpopulations

Research question 1

Table 21: Results (morbidity, dichotomous, time to event - supplementary presentation) – RCT, direct comparison: lecanemab vs. placebo (research question 1)

Study outcome category outcome	Lecanemab N	Lecanemab median time to event in months [95% CI] patients with event n (%)	placebo N	placebo median time to event in months [95% CI] patients with event n (%)	Lecanemab vs. placebo HR [95% CI]; p-value[a]
CLARITY AD					
Morbidity					
Symptoms (CDR-SB – time to first deterioration up to Month 18[b]	*242*	*NA [18.9; NC]* *28 (11.6)*	*240*	*NA* *38 (15.8)*	*0.64 [0.39; 1.04]; 0.073*
Symptoms (CDR-SB – time to confirmed deterioration up to Month 18[c]	*242*	*NA* *18 (7.4)*	*240*	*NA* *16 (6.7)*	*1.03 [0.52; 2.02]; 0.935*
	N	**Patients with event n (%)**	**N**	**Patients with event n (%)**	**RR [95% CI]; p-value**
Symptoms (CDR-SB – deterioration at Month 18[d])	216	22 (10.2)	217	25 (11.5)	0.85 [0.51; 1.44]; 0.547[e]

a. Effect, CI and p-value: Cox proportional hazards model with treatment, subpopulation, AChEI use at baseline, ApoE-ε4 status and region as covariable.
b. An increase of the CDR-SB by ≥ 2.7 points (15% of the scale range) from baseline is considered a clinically relevant deterioration (score range of the scale: 0 to 18).
c. An increase of the CDR-SB by ≥ 2.7 points (15% of the scale range) from baseline that was confirmed in a consecutive visit is considered a clinically relevant deterioration (score range of the scale: 0 to 18). Patients with a first deterioration without follow-up recording (i.e. with a first deterioration at Month 18 or with subsequent treatment discontinuation) were censored. For further explanations, see Chapter 2 of this addendum.
d. An increase of the CDR-SB by ≥ 2.7 points (15% of the scale range) from baseline is considered a clinically relevant deterioration (score range of the scale: 0 to 18).
e. Effect, CI and p-value: logistic regression model stratified by subpopulation, AChEI use at baseline, ApoE-ε4 status and region.

AChEI: acetylcholinesterase inhibitors; ApoE ε4: apolipoprotein E ε4; CDR-SB: Clinical Dementia Rating-Sum of Boxes; CI: confidence interval; HR: hazard ratio; n: number of patients with event; N: number of analysed patients; NA: not achieved; RCT: randomized controlled trial

Table 22: Data on response rates for the CDR-SB in the course of the study – RCT, direct comparison: lecanemab versus placebo (research question 1)

Study observation time point	Patients with survey, n (%)	
	lecanemab Na = 242	placebo Na = 240
CLARITY AD		
Baseline	242 (100)	240 (100)
Week 13	234 (96.7)	235 (97.9)
Week 27	233 (96.3)	231 (96.3)
Week 39	229 (94.6)	228 (95.0)
Week 53	228 (94.2)	219 (91.3)
Week 65	221 (91.3)	218 (90.8)
Week 79	216 (89.3)	217 (90.4)

a. ITT-FAS+: patients who received at least one dose of the respective treatment and for whom a baseline value and at least one post-baseline questionnaire evaluation in the CDR were available.

CDR: Clinical Dementia Rating; CDR-SB: Clinical Dementia Rating – Sum of Boxes; n: number of patients with recordings; N: number of analysed patients (ITT-FAS+); RCT: randomized controlled trial

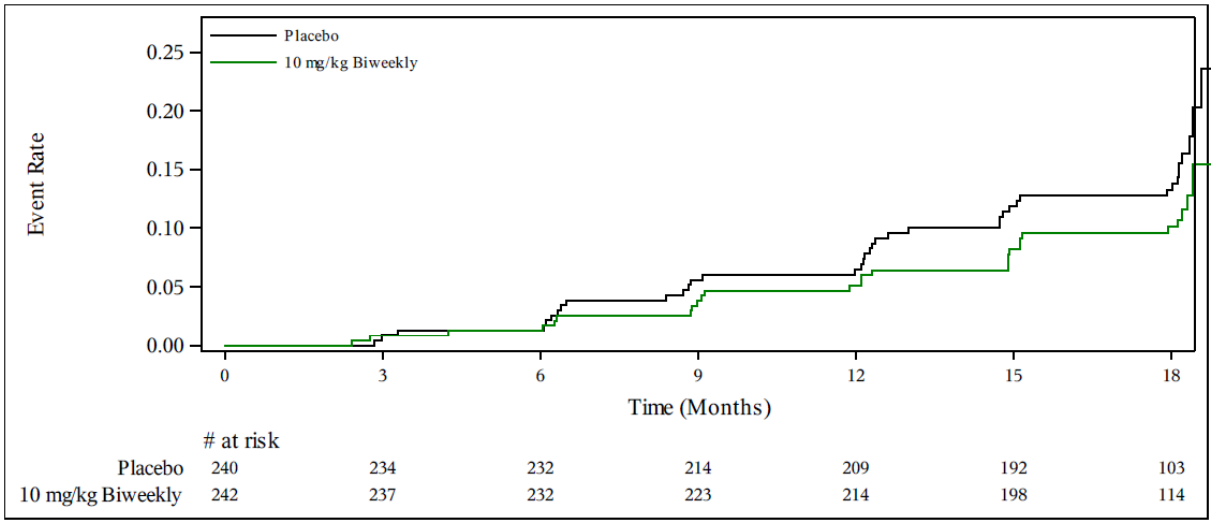


Figure 3: Kaplan-Meier curve for the outcome symptoms (CDR-SB) in the CLARITY AD study – time to first deterioration up to Month 18 (research question 1)

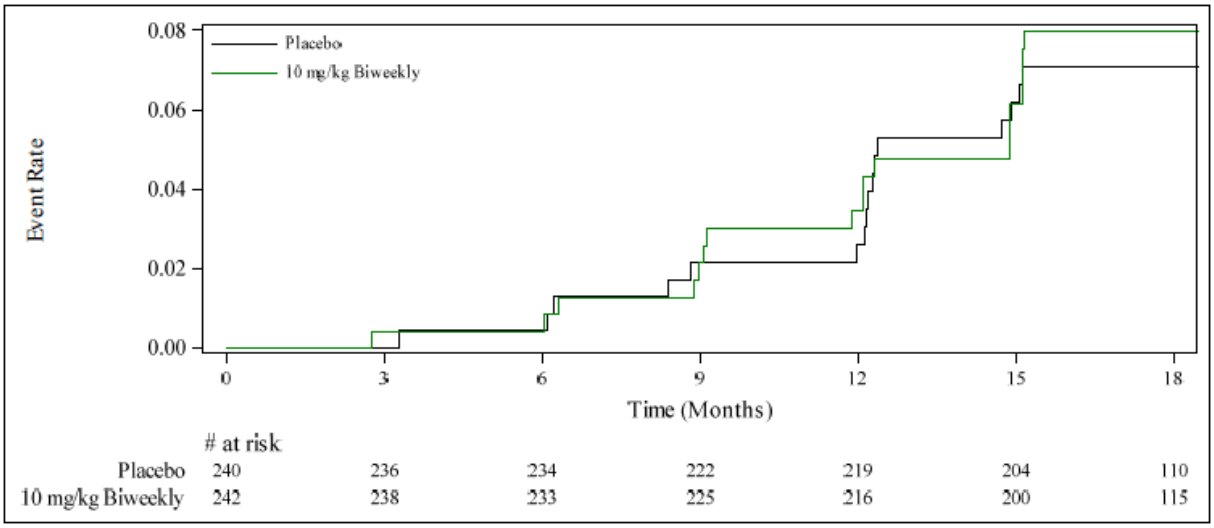


Figure 4: Kaplan-Meier curve for the outcome symptoms (CDR-SB) in the CLARITY AD study – time to confirmed deterioration up to Month 18 (research question 1)

Research question 2

Table 23: Results (morbidity, dichotomous, time to event - supplementary presentation) – RCT, direct comparison: lecanemab vs. placebo (research question 2)

Study outcome category outcome	Lecanemab N	Lecanemab median time to event in months [95% CI] patients with event n (%)	placebo N	placebo median time to event in months [95% CI] patients with event n (%)	Lecanemab vs. placebo HR [95% CI]; p-value[a]
CLARITY AD					
Morbidity					
Symptoms (CDR-SB – time to first deterioration up to Month 18[b]	*136*	*NA [18.3; NC]* *37 (27.2)*	*137*	*NA [17.9; NC]* *55 (40.1)*	*0.66 [0.43; 0.998]; 0.049*
Symptoms (CDR-SB – time to confirmed deterioration up to Month 18[c]	*136*	*NA* *20 (14.7)*	*137*	*NA* *43 (31.4)*	*0.46 [0.27; 0.79]; 0.003*
	N	**Patients with event n (%)**	**N**	**Patients with event n (%)**	**RR [95% CI]; p-value**
Symptoms (CDR-SB – deterioration at Month 18[d])	103	28 (27.2)	115	39 (33.9)	0.84 [0.56; 1.27]; 0.410[e]

a. Effect, CI and p-value: Cox proportional hazards model with treatment, subpopulation, AChEI use at baseline, ApoE-ε4 status and region as covariable.
b. An increase of the CDR-SB by ≥ 2.7 points (15% of the scale range) from baseline is considered a clinically relevant deterioration (score range of the scale: 0 to 18).
c. An increase of the CDR-SB by ≥ 2.7 points (15% of the scale range) from baseline that was confirmed in a consecutive visit is considered a clinically relevant deterioration (score range of the scale: 0 to 18). Patients with a first deterioration without follow-up recording (i.e. with a first deterioration at Month 18 or with subsequent treatment discontinuation) were censored. For further explanations, see Chapter 2 of this addendum.
d. An increase of the CDR-SB by ≥ 2.7 points (15% of the scale range) from baseline is considered a clinically relevant deterioration (score range of the scale: 0 to 18).
e. Effect, CI and p-value: logistic regression model stratified by subpopulation, AChEI use at baseline, ApoE-ε4 status and region.

AChEI: acetylcholinesterase inhibitors; ApoE ε4: apolipoprotein E ε4; CI: confidence interval; HR: hazard ratio; n: number of patients with event; N: number of analysed patients; NA: not achieved; RCT: randomized controlled trial

Table 24: Data on response rates for the CDR-SB in the course of the study – RCT, direct comparison: lecanemab + AChEI versus placebo + AChEI (research question 2)

Study observation time point	Patients with survey, n (%)	
	lecanemab Na = 136	placebo Na = 137
CLARITY AD		
Baseline	136 (100)	137 (100)
Week 13	129 (94.9)	131 (95.6)
Week 27	118 (86.8)	129 (94.2)
Week 39	116 (85.3)	128 (93.4)
Week 53	111 (81.6)	122 (89.1)
Week 65	106 (77.9)	119 (86.9)
Week 79	103 (75.7)	115 (83.9)

a. ITT-FAS+: patients who received at least one dose of the respective treatment and for whom a baseline value and at least one post-baseline questionnaire evaluation in the CDR were available.

CDR: Clinical Dementia Rating; CDR-SB: Clinical Dementia Rating – Sum of Boxes; n: number of patients with recordings; N: number of analysed patients (ITT-FAS+); RCT: randomized controlled trial

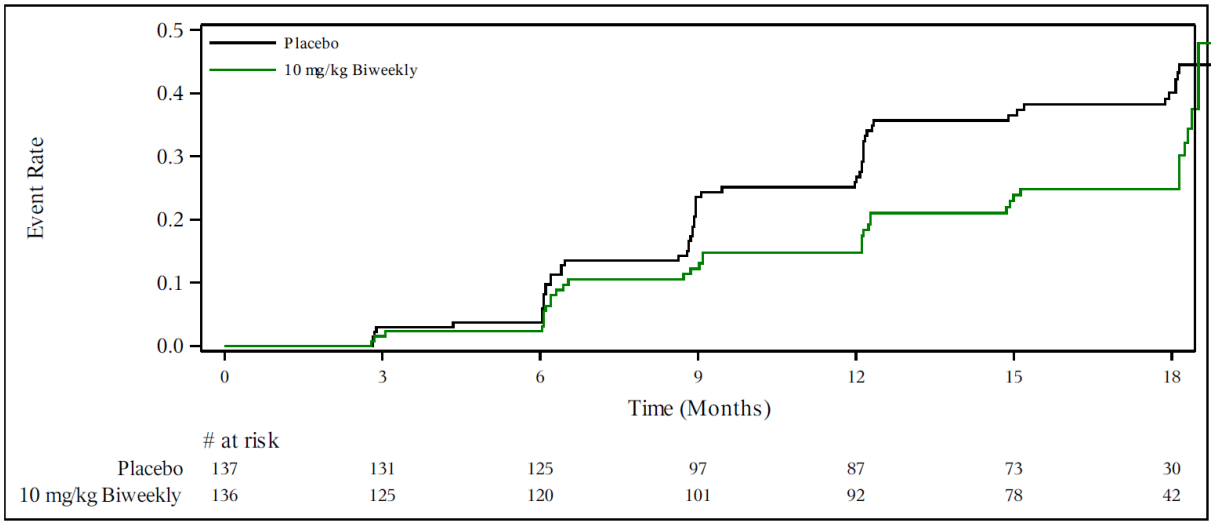


Figure 5: Kaplan-Meier curve for the outcome symptoms (CDR-SB) in the CLARITY AD study – time to first deterioration up to Month 18 (research question 2)

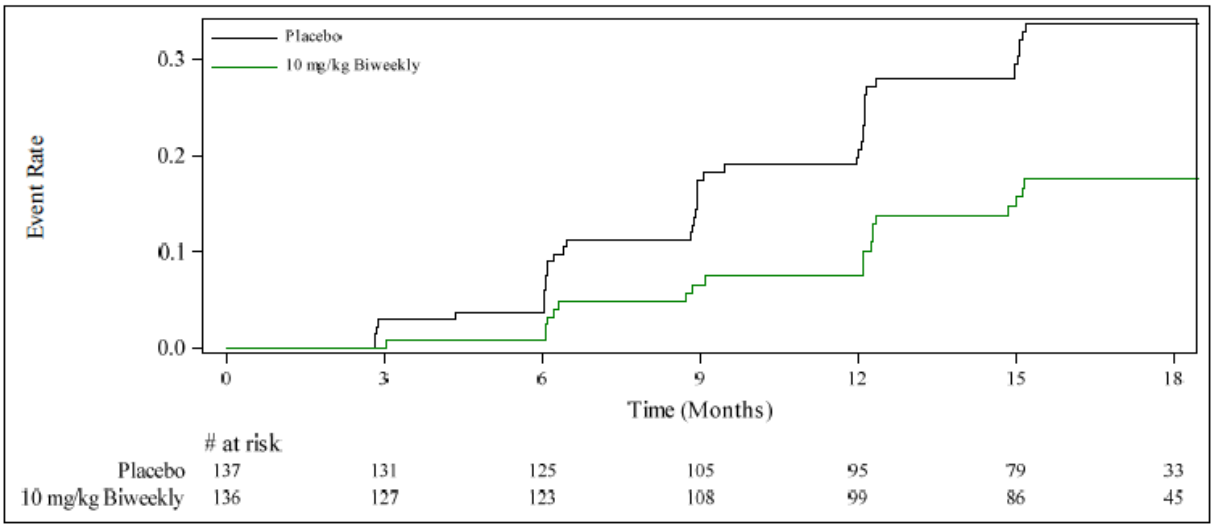
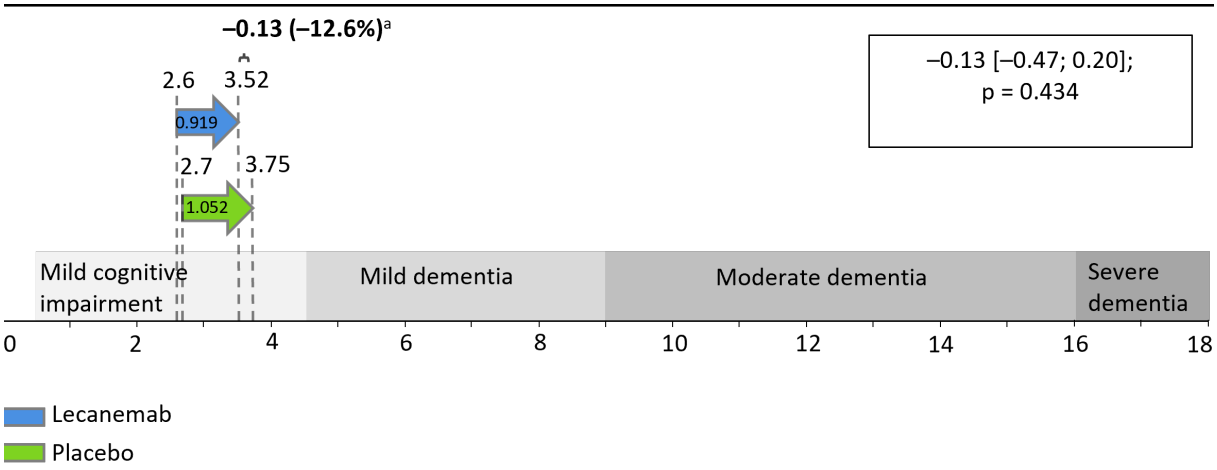


Figure 6: Kaplan-Meier curve for the outcome symptoms (CDR-SB) in the CLARITY AD study – time to confirmed deterioration up to Month 18 (research question 2)

B.2 Informative graphs on the CDR-SB and its domains for the relevant subpopulations

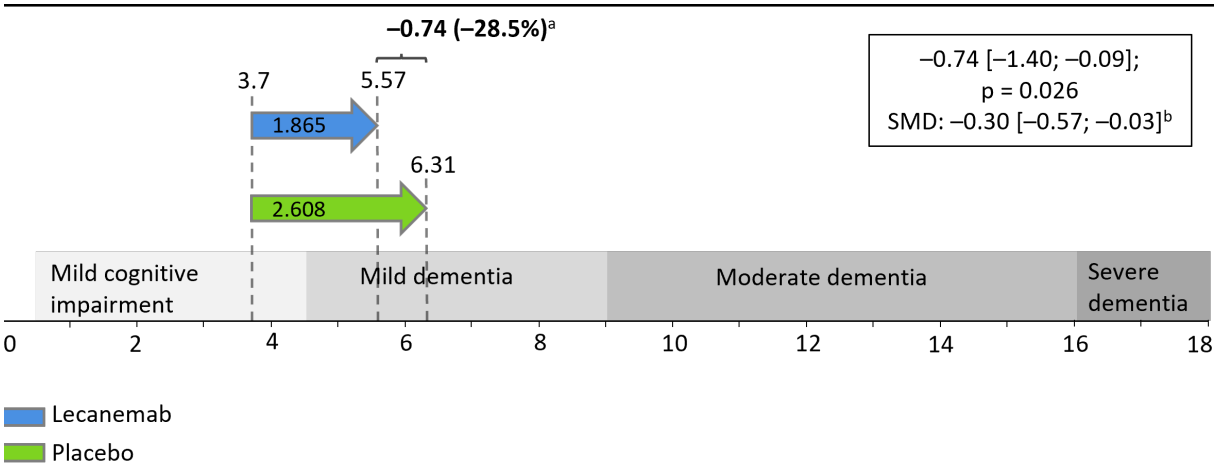
In dossier assessment A25-111, various informative graphs were presented to illustrate the results of continuous analyses on the outcome symptoms (CDR-SB) presented as supplementary information. However, data for the relevant subpopulations were not available for all graphs. With the data subsequently submitted with the commenting procedure, these can now be presented in full.

Figure 10 illustrates that, on average, there are only very small numerical changes (from baseline to Month 18) between the treatment groups in each of the individual domains of the CDR-SB. The trend plots for the domains in Figure 11 also illustrate that lecanemab tends to result in lower scores in the CDR-SB for the functional domains rather than for the cognitive domains. Here, too, the numerical differences are small.



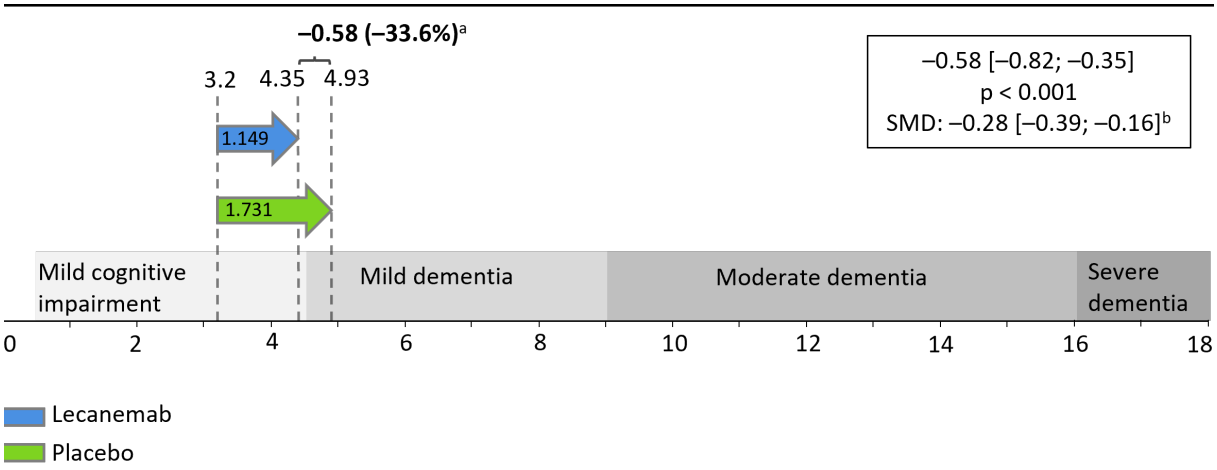
a. Differences in mean values vs. 18 months in the approval-compliant MCI population without anti-dementia drugs. The change in the CDR-SB score in the intervention arm was 12.6% lower than in the control arm (calculated as [change intervention arm–change control arm/change control arm]).
ApoE ε4: apolipoprotein E ε4; CDR-SB: Clinical Dementia Rating – Sum of Boxes

Figure 7: Change in CDR-SB from baseline to Month 18 in the approval-compliant MCI population without anti-dementia drugs (research question 1)



a. Differences in mean values vs. 18 months in the approval-compliant population with mild Alzheimer's dementia with AChEI therapy. The change in the CDR-SB score in the intervention arm was 28.5% lower than in the control arm (calculated as [change intervention arm–change control arm/change control arm]).
b. As the 95% CI of the SMD was not fully below the irrelevance threshold of −0.2, it cannot be inferred that the effect is relevant.
AChEI: acetylcholinesterase inhibitors; ApoE ε4: apolipoprotein E ε4; CDR-SB: Clinical Dementia Rating – Sum of Boxes; CI: confidence interval; SMD: standardized mean difference

Figure 8: Change in CDR-SB from baseline to Month 18 in the approval-compliant population with mild Alzheimer's dementia with AChEI therapy (research question 2)



a. Differences in mean values vs. 18 months in the ITT-FAS+ population. The change in the CDR-SB score in the intervention arm was 33.6% lower than in the control arm (calculated as [change intervention arm–change control arm/change control arm]).

b. As the 95% CI of the SMD was not fully below the irrelevance threshold of −0.2, it cannot be inferred that the effect is relevant.

CDR-SB: Clinical Dementia Rating – Sum of Boxes; CI: confidence interval; ITT-FAS+: patients who received at least one dose of the respective treatment and for whom a baseline value and at least one post-baseline questionnaire evaluation in the CDR were available; SMD: Standardized Mean Difference

Figure 9: Change in CDR-SB from baseline to Month 18 in the lecanemab approval population of the CLARITY AD study (without consideration of the concomitant medication).

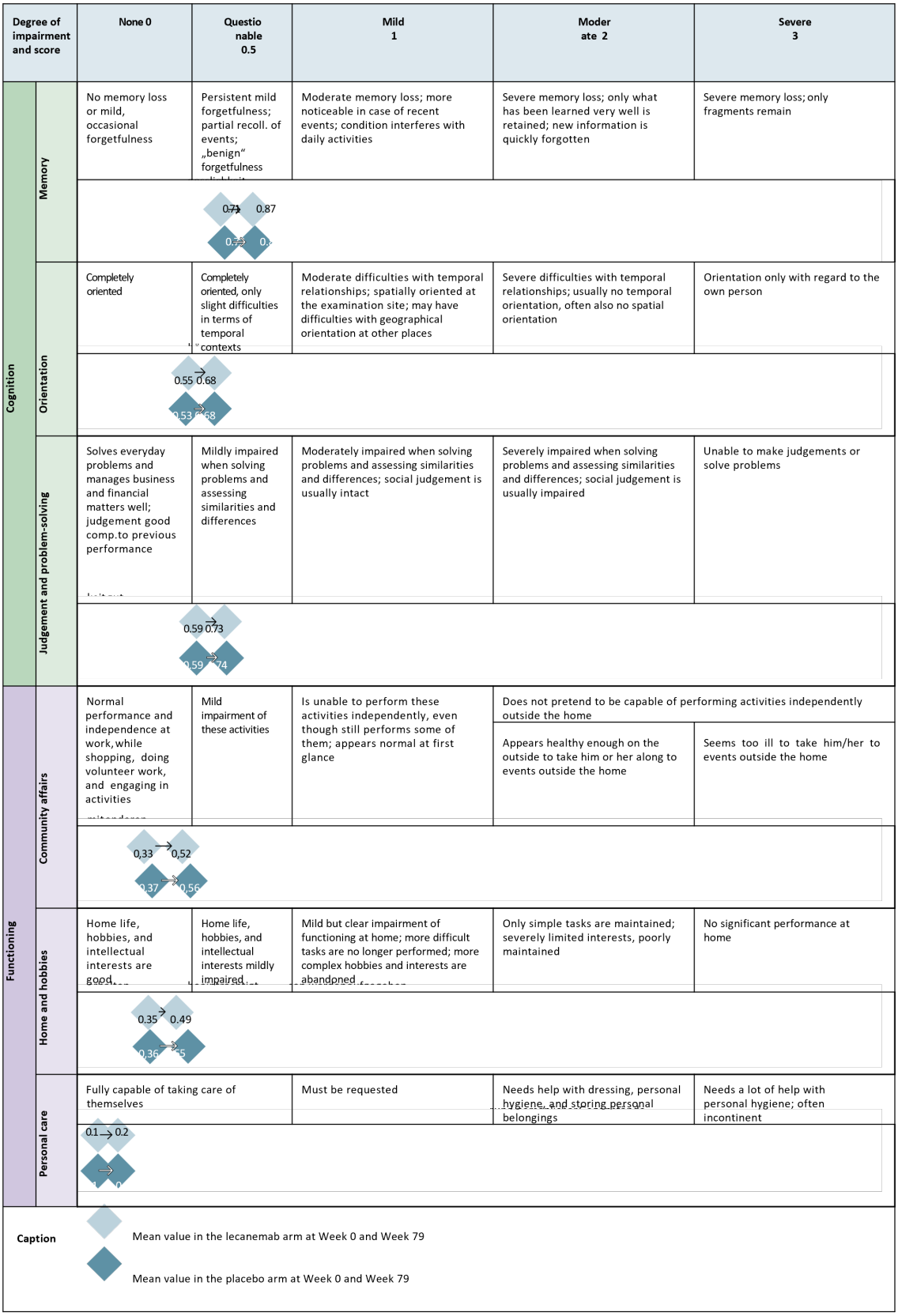


Figure 10: Change in the domains of the CDR-SB from baseline to Month 18 in the approval-compliant MCI population without anti-dementia drugs (research question 1)

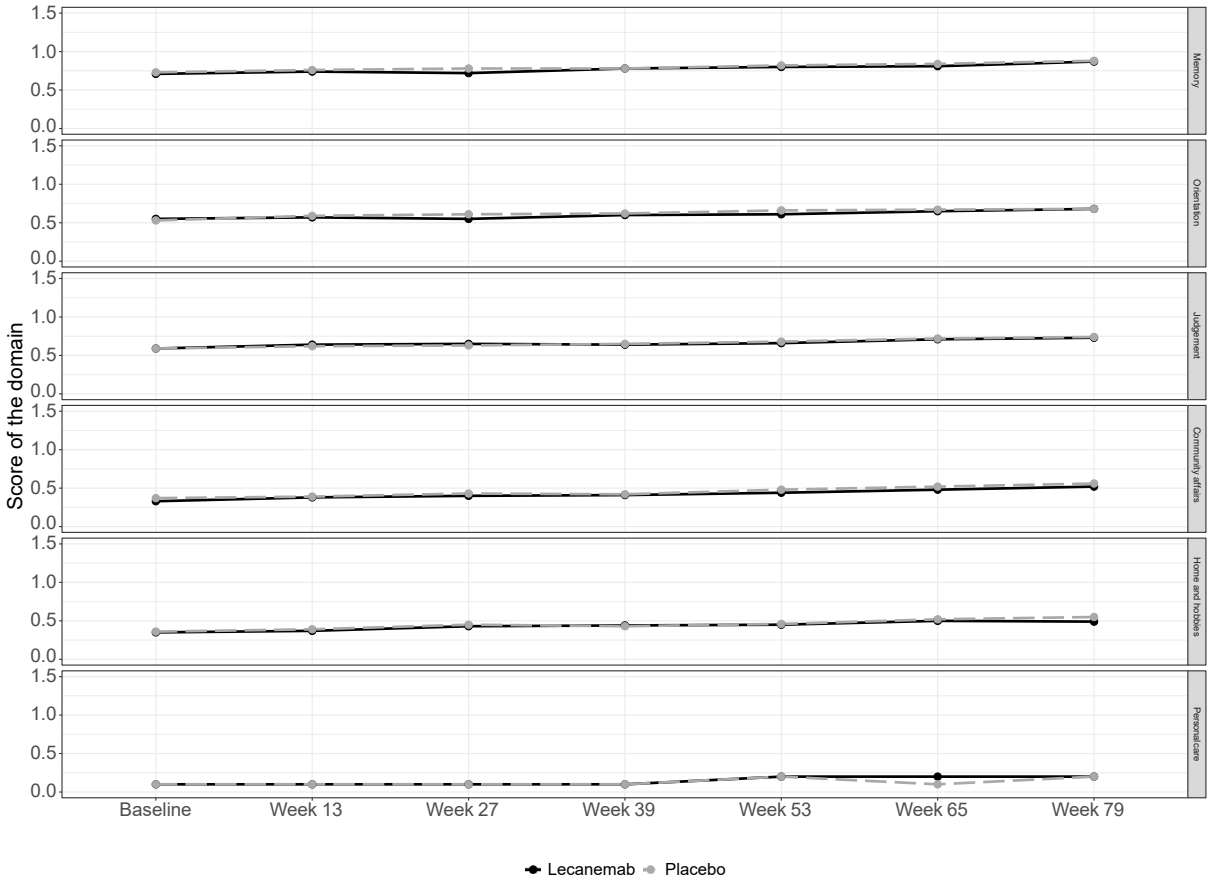


Figure 11: Change in the domains of the CDR-SB over time from baseline to Month 18 in the approval-compliant MCI population without anti-dementia drugs (research question 1) (Presentation of a section of the full scale range from 0 to 3 for each category)

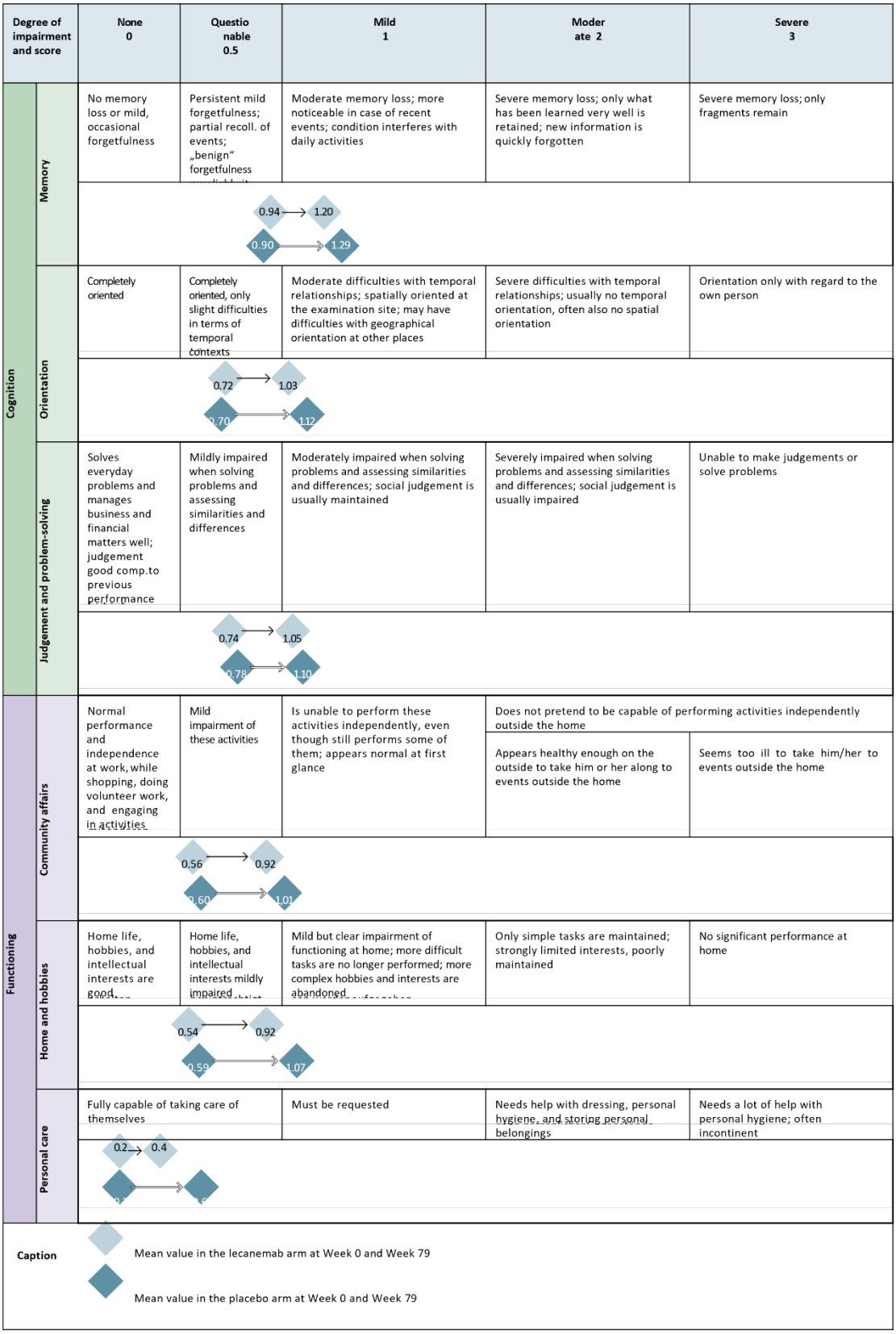


Figure 12: Change in the domains of the CDR-SB from baseline to Month in the approval-compliant population with mild Alzheimer's dementia with AChEI therapy (research question 2)

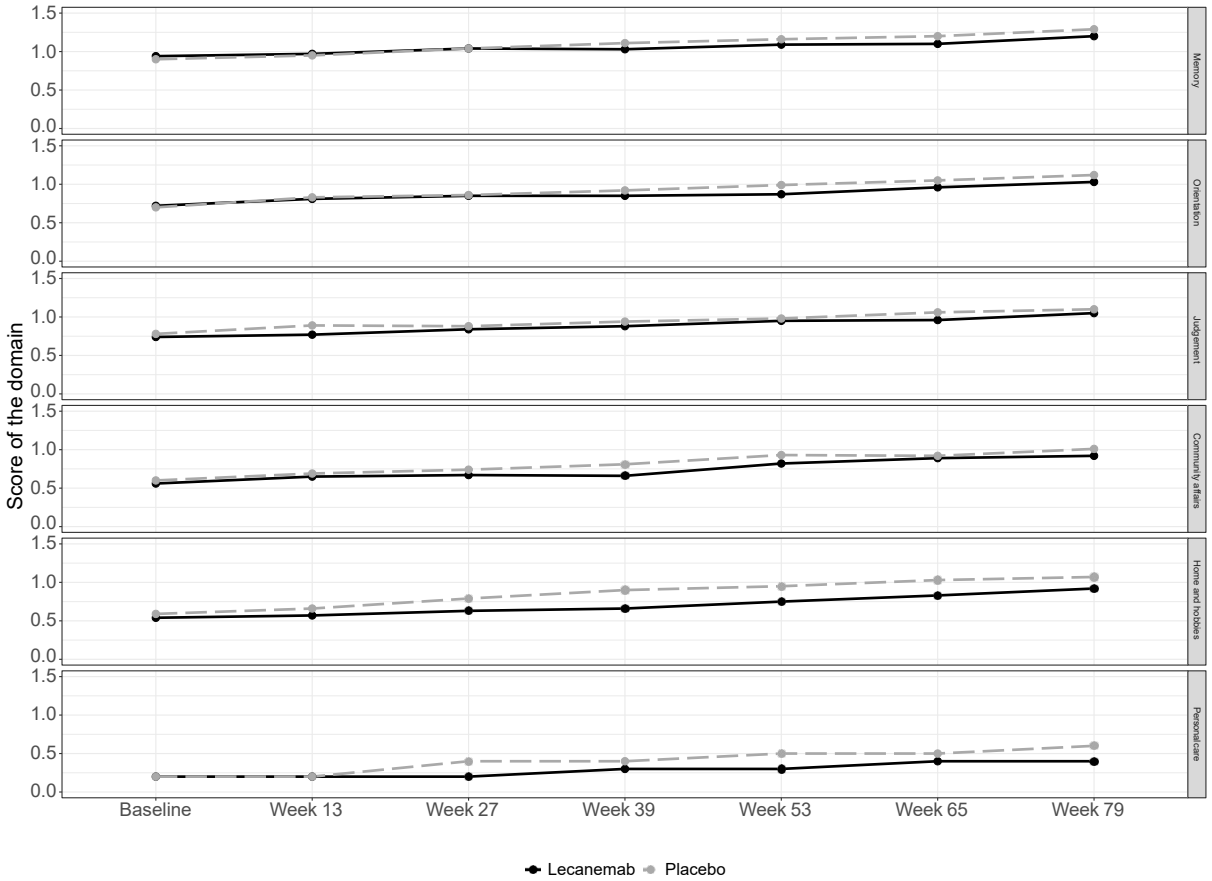


Figure 13: Change in the domains of the CDR-SB from baseline to Month 18 in the approval-compliant population with mild Alzheimer's dementia with AChEI therapy (research question 2) (Presentation of a section of the full scale range from 0 to 3 for each category)

Appendix C Forest plots on supplementary analyses of various outcomes for various populations

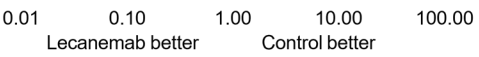
As described in dossier assessment A25-111 [1], the dossier contains only incomplete information for the relevant subpopulations and for other approval-compliant populations. The company subsequently submitted the relevant information as part of the commenting procedure [2], meaning that questions regarding the data situation on patients not treated in compliance with the ACT that had remained open particularly in the dossier assessment can now be addressed.

The forest plots below illustrate the available results for various populations of the CLARITY AD study, including the relevant subpopulations (according to research question 1 and research question 2).

The forest plots presented in dossier assessment A25-111 were based on unstratified analyses. Stratified analyses have now been presented as part of the comments. For the primary outcome CDR-SB, both analyses are presented as examples in this addendum (compare Figure 14 and Figure 15). An interpretation of the data presented here can be found in Section 2.1.3.2 and Section 2.2.3.2.

Clarity AD
CDR-SB stratified

Indication Population	Lecanemab n/N	Control n/N	RR (95% CI)	RR	95% CI
MCI + AD					
Total population	109/714	155/757		0.80	[0.65, 0.99]
Approval population	85/576	133/608		0.73	[0.57, 0.93]
Research question 1 + 2 (ACT-compl.)	50/319	64/332		—	—
Not ACT-compliant	35/257	69/276		—	—
MCI					
MCI population	45/460	76/487		0.63	[0.45, 0.88]
MCI population (ACT-compliant)	38/374	66/396		0.63	[0.44, 0.91]
Research question 1 (untreated)	22/216	25/217		0.85	[0.50, 1.43]
Not ACT-compliant (with AChEI)	14/126	31/139		0.52	[0.29, 0.92]
Not ACT-compliant (with memantine)	2/32	10/40		0.29	[0.07, 1.25]
AD					
Mild AD population	64/254	79/270		0.92	[0.70, 1.22]
Mild AD population (approval-compl.)	47/202	67/212		0.80	[0.58, 1.10]
Research question 2 (with AChEI)	28/103	39/115		0.84	[0.56, 1.27]
Not ACT-compliant (untreated)	10/71	16/60		0.55	[0.27, 1.11]
Not ACT-compliant (with meman.)	9/28	12/37		—	—



The terms approval population and approval-compliant refer to the marketing authorization of lecanemab. The term untreated refers to concomitant medication.

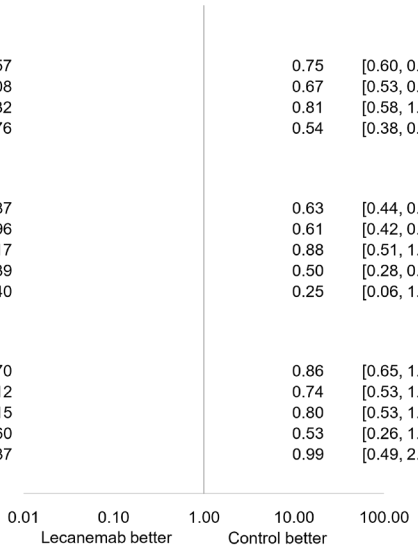
Effect and CI are based on a logistic regression model stratified by subpopulation, AChEI use at baseline, ApoE-ε4 status and region. Where stratified analyses for effect and CI were not available or could not be calculated, these are not shown. The results for the event rates (n/N) for 'research questions 1 + 2 (ACT-compliant)' and 'non-ACT-compliant' (first block) are based on the Institute's calculations.

AChEI: acetylcholinesterase inhibitors; ACT: appropriate comparator therapy; AD: mild Alzheimer's dementia; ApoE-ε4: apolipoprotein E ε4; CDR-SB: Clinical Dementia Rating – Sum of Boxes; CI: confidence interval; MCI: mild cognitive impairment; N: number of analysed patients; n: number of patients with event; RR: relative risk

Figure 14: Forest plots for the outcome symptoms (CDR-SB) – deterioration by ≥ 2.7 points at Month 18 of the CLARITY AD study (stratified analyses)

Study CLARITY AD
CDR-SB unstratified

Indication Population	Lecanemab n/N	Control n/N	RR (95% CI)	RR	95% CI
MCI + AD					
Total population	109/714	155/757		0.75	[0.60, 0.93]
Approval population	85/576	133/608		0.67	[0.53, 0.86]
Research question 1 + 2 (ACT-com.)	50/319	64/332		0.81	[0.58, 1.14]
Not ACT-compliant	35/257	69/276		0.54	[0.38, 0.79]
MCI					
MCI population	45/460	76/487		0.63	[0.44, 0.89]
MCI population (approval-compliant)	38/374	66/396		0.61	[0.42, 0.89]
Research question 1 (untreated)	22/216	25/217		0.88	[0.51, 1.52]
(not ACT-compliant with AChEI)	14/126	31/139		0.50	[0.28, 0.89]
Not ACT-compliant (with memantine)	2/32	10/40		0.25	[0.06, 1.06]
AD					
Mild AD population	64/254	79/270		0.86	[0.65, 1.14]
Mild AD population (approval-compliant)	47/202	67/212		0.74	[0.53, 1.01]
Research question 2 (with AChEI)	28/103	39/115		0.80	[0.53, 1.20]
Not ACT-compliant (untreated)	10/71	16/60		0.53	[0.26, 1.08]
Not ACT-compliant (with memantine)	9/28	12/37		0.99	[0.49, 2.02]



The terms approval population and approval-compliant refer to the marketing authorization of lecanemab. The term untreated refers to concomitant medication.

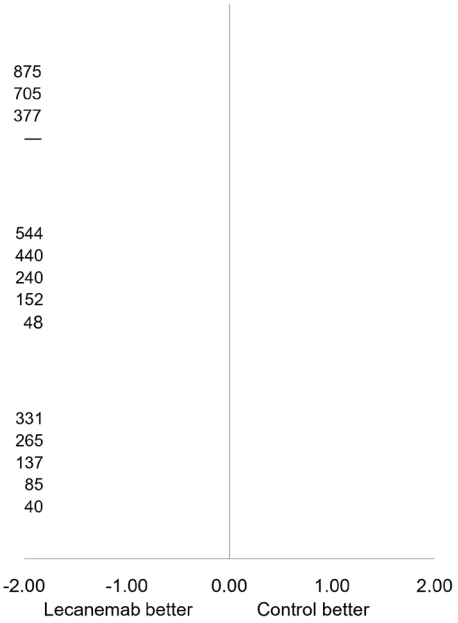
Institute's calculation of effect and CI (asymptotic). The results on the event rates (n/N) for 'research questions 1 + 2 (ACT-compliant)' and 'non-ACT-compliant' (first block) are based on the Institute's calculations.

AChEI: acetylcholinesterase inhibitors; ACT: appropriate comparator therapy; AD: mild Alzheimer's dementia; ApoE-ε4: apolipoprotein E ε4; CDR-SB: Clinical Dementia Rating – Sum of Boxes; CI: confidence interval; MCI: mild cognitive impairment; N: number of analysed patients; n: number of patients with event; RR: relative risk

Figure 15: Forest plots on the outcome symptoms (CDR-SB) – deterioration by ≥ 2.7 points at Month 18 of the CLARITY AD study (stratified analyses)

Clarity AD
CDR-SB SMD

Indication Population	Lecanemab N	Control N	SMD (95% CI)	SMD	95% CI
MCI + AD					
Total population	859	875		-0.21	[-0.31, -0.10]
Approval population	689	705		-0.28	[-0.39, -0.16]
Research question 1 + 2 (ACT-com.)	378	377		-0.15	[-0.31, 0.01]
Not ACT-compliant	—	—		—	—
MCI					
MCI population	528	544		-0.19	[-0.32, -0.06]
MCI population (approval-compliant)	423	440		-0.22	[-0.36, -0.07]
Research question 1 (untreated)	242	240		-0.07	[-0.26, 0.12]
Not ACT-compliant (with AChEI)	140	152		-0.37	[-0.61, -0.12]
Not ACT-compliant (with memantine)	41	48		-0.38	[-0.85, 0.09]
AD					
Mild AD population	331	331		-0.23	[-0.41, -0.06]
Mild AD population (ACT-compliant)	266	265		-0.37	[-0.56, -0.17]
Research question 2 (with AChEI)	136	137		-0.30	[-0.57, -0.03]
Not ACT-compliant (untreated)	91	85		-0.65	[-1.01, -0.30]
Not ACT-compliant (with memantie)	39	40		-0.06	[-0.55, 0.43]

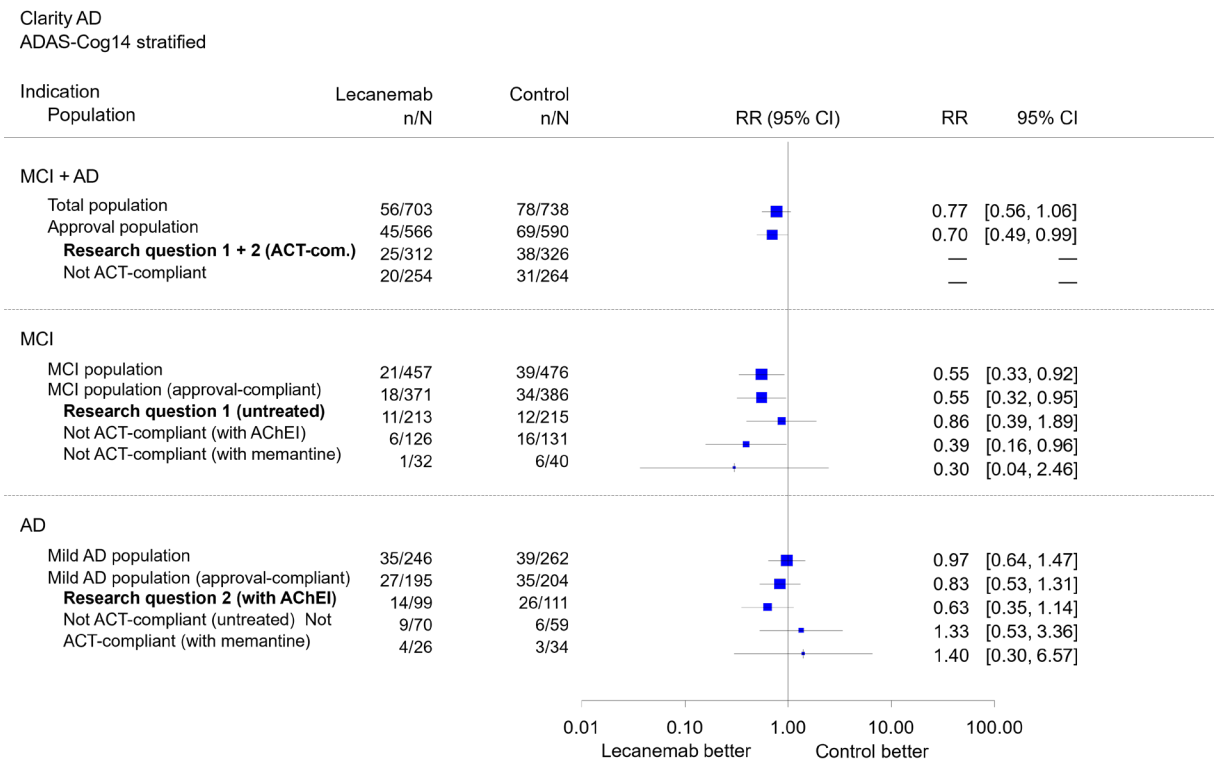


The terms approval population and approval-compliant refer to the marketing authorization of lecanemab. The term untreated refers to concomitant medication.

Effect and CI are based on the SMD with the corresponding 95% CI; these were considered when assessing the relevance of the result. If the 95% CI of the SMD is not fully below the irrelevance threshold of −0.2, it cannot be inferred that the effect is relevant. The analyses are each based on an MMRM with treatment group, region, visit, subpopulation, ApoE-ε4 status, AChEI use at baseline, baseline value, interactions treatment group*visit and baseline value*visit. The results for 'research question 1 and 2 (ACT-compliant)' are based on the Institute's calculations (meta-analysis with fixed effect).

AAChEI: acetylcholinesterase inhibitors; ACT: appropriate comparator therapy; AD: mild Alzheimer's dementia; CI: confidence interval; MCI: mild cognitive impairment; MMRM: mixed-effects model with repeated measures; N: number of analysed patients; SMD: standardized mean difference

Figure 16: Forest plots on the outcome symptoms (CDR-SB) on the continuous analyses of the CLARITY AD study

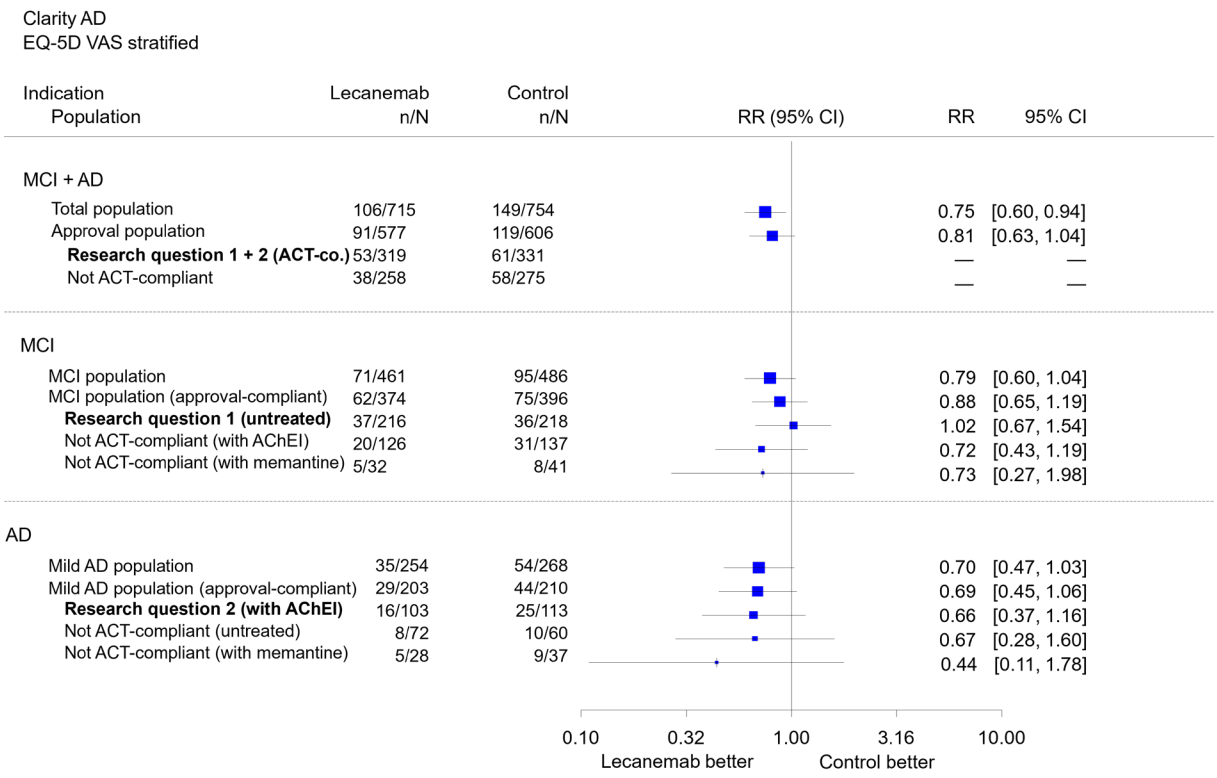


The terms approval population and approval-compliant refer to the marketing authorization of lecanemab. The term untreated refers to concomitant medication.

Effect and CI are based on a logistic regression model stratified by subpopulation, AChEI use at baseline, ApoE-ε4 status and region. Where stratified analyses for effect and CI were not available or could not be calculated, these are not shown. The results for the event rates (n/N) for 'research questions 1 + 2 (ACT-compliant)' and 'non-ACT-compliant' (first block) are based on the Institute's calculations.

AChEI: acetylcholinesterase inhibitors; ACT: appropriate comparator therapy; AD: mild Alzheimer's dementia; ApoE-ε4: apolipoprotein E ε4; CDR-SB: Clinical Dementia Rating – Sum of Boxes; CI: confidence interval; MCI: mild cognitive impairment; N: number of analysed patients; n: number of patients with event; RR: relative risk

Figure 17: Forest plots on the outcome cognition (ADAS-Cog14) – deterioration by ≥ 13.5 points at Month 18 of the CLARITY AD study

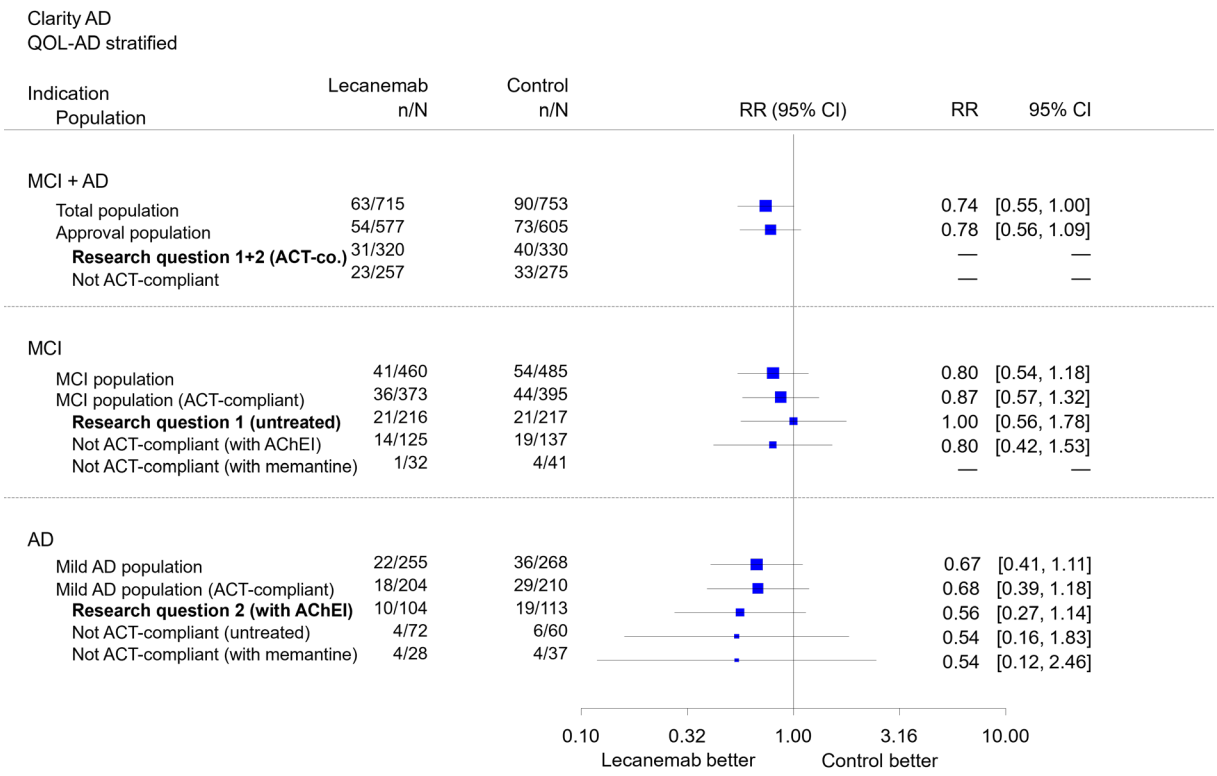


The terms approval population and approval-compliant refer to the marketing authorization of lecanemab. The term untreated refers to concomitant medication.

Effect and CI are based on a logistic regression model stratified by subpopulation, AChEI use at baseline, ApoE-ε4 status and region. Where stratified analyses for effect and CI were not available or could not be calculated, these are not shown. The results for the event rates (n/N) for 'research questions 1 + 2 (ACT-compliant)' and 'non-ACT-compliant' (first block) are based on the Institute's calculations.

AChEI: acetylcholinesterase inhibitors; ACT: appropriate comparator therapy; AD: mild Alzheimer's dementia; ApoE-ε4: apolipoprotein E ε4; CDR-SB: Clinical Dementia Rating – Sum of Boxes; CI: confidence interval; MCI: mild cognitive impairment; N: number of analysed patients; n: number of patients with event; RR: relative risk

Figure 18: Forest plots on the outcome health status (EQ-5D VAS) – deterioration by ≥ 15 points at Month 18 of the CLARITY AD study



The terms approval population and approval-compliant refer to the marketing authorization of lecanemab. The term untreated refers to concomitant medication.

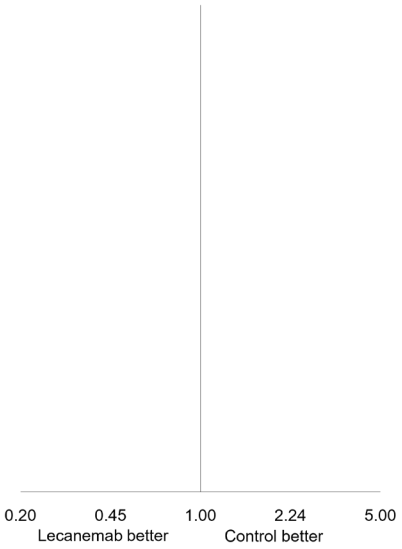
Effect and CI are based on a logistic regression model stratified by subpopulation, AChEI use at baseline, ApoE-ε4 status and region. Where stratified analyses for effect and CI were not available or could not be calculated, these are not shown. The results for the event rates (n/N) for 'research questions 1 + 2 (ACT-compliant)' and 'non-ACT-compliant' (first block) are based on the Institute's calculations.

AChEI: acetylcholinesterase inhibitors; ACT: appropriate comparator therapy; AD: mild Alzheimer's dementia; ApoE-ε4: apolipoprotein E ε4; CDR-SB: Clinical Dementia Rating – Sum of Boxes; CI: confidence interval; MCI: mild cognitive impairment; N: number of analysed patients; n: number of patients with event; RR: relative risk

Figure 19: Forest plots on the outcome health-related quality of life (QOL-AD) – deterioration by ≥ 5.85 points at Month 18 of the CLARITY AD study

Study CLARITY AD
SAEs unstratified

Indication Population	Lecanemab n/N	Control n/N	RR	95% CI
MCI + AD				
Total population	126/898	101/897	1.25	[0.98, 1.59]
Approval population	104/721	82/724	1.27	[0.97, 1.67]
Research question 1 + 2 (ACT-com.)	57/391	42/383	1.33	[0.92, 1.93]
Not ACT-compliant	47/330	40/341	1.21	[0.82, 1.80]
MCI				
MCI population	79/552	66/555	1.20	[0.89, 1.63]
MCI population (approval-compliant)	65/443	53/448	1.24	[0.88, 1.74]
Research question 1 (untreated)	37/252	28/245	1.28	[0.81, 2.03]
Not ACT-compliant (with AChEI)	23/149	20/155	1.20	[0.69, 2.08]
Not ACT-compliant (with memantine)	5/42	5/48	1.14	[0.36, 3.68]
AD				
Mild AD population	47/346	35/342	1.33	[0.88, 2.00]
Mild AD population (approval-compliant)	39/278	29/276	1.34	[0.85, 2.10]
Research question 2 (with AChEI)	20/139	14/138	1.42	[0.75, 2.69]
Not ACT-compliant (untreated)	12/98	9/92	1.25	[0.55, 2.83]
Not ACT-compliant (with memantine)	7/41	6/46	1.31	[0.48, 3.58]



The terms approval population and approval-compliant refer to the marketing authorization of lecanemab. The term untreated refers to concomitant medication.

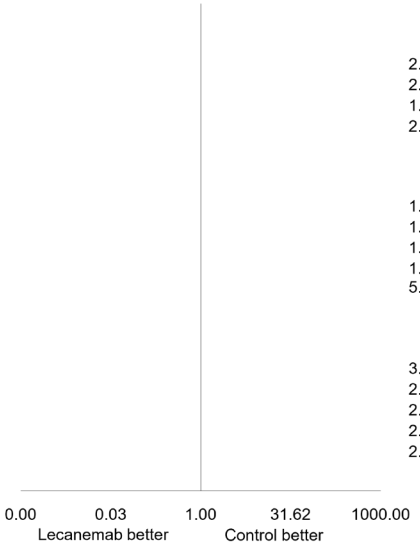
Institute's calculation of effect and CI (asymptotic). The results on the event rates (n/N) for 'research questions 1 + 2 (ACT-compliant)' and 'non-ACT-compliant' (first block) are based on the Institute's calculations.

AAChEI: acetylcholinesterase inhibitors; ACT: appropriate comparator therapy; AD: mild Alzheimer's dementia; CI: confidence interval; MCI: mild cognitive impairment; N: number of analysed patients; n: number of patients with event; RR: relative risk; SAE: serious adverse event

Figure 20: Forest plots for the outcome SAE in the CLARITY AD study

Study CLARITY AD
Discontinuation due to AEs, unstratified

Indication Population	Lecanemab n/N	Control n/N	RR	95% CI
MCI + AD				
Total population	64/898	28/897	2.28	[1.48, 3.53]
Approval population	42/721	21/724	2.01	[1.20, 3.36]
Research question 1 + 2 (ACT-compliant)	21/391	11/383	1.87	[0.91, 3.83]
Not ACT-compliant	21/330	10/341	2.17	[1.04, 4.54]
MCI				
MCI population	29/552	17/555	1.72	[0.95, 3.08]
MCI population (approval-compliant)	18/443	11/448	1.65	[0.79, 3.46]
Research question 1 (untreated)	11/252	7/245	1.53	[0.60, 3.88]
Not ACT-compliant (with AChEI)	5/149	4/155	1.30	[0.36, 4.75]
Not ACT-compliant (with meman.)	2/42	0/48	5.70	[0.28, 115.43]
AD				
Mild AD population	35/346	11/342	3.15	[1.62, 6.09]
Mild AD population (approval-compliant)	24/278	10/276	2.38	[1.16, 4.89]
Research question 2 (with AChEI)	10/139	4/138	2.48	[0.80, 7.72]
Not ACT-compliant (untreated)	8/98	3/92	2.50	[0.68, 9.15]
Not ACT-compliant (with mema.)	6/41	3/46	2.24	[0.60, 8.40]



The terms approval population and approval-compliant refer to the marketing authorization of lecanemab. The term untreated refers to concomitant medication.

Institute's calculation of effect and CI (asymptotic). The results on the event rates (n/N) for ‘research questions 1 + 2 (ACT-compliant)’ and ‘non-ACT-compliant’ (first block) are based on the Institute's calculations.

AChEI: acetylcholinesterase inhibitors; ACT: appropriate comparator therapy; AD: mild Alzheimer’s dementia; AE: adverse event; CI: confidence interval; MCI: mild cognitive impairment; N: number of analysed patients; n: number of patients with event; RR: relative risk

Figure 21: Forest plots for the outcome discontinuation due to AEs in the CLARITY AD study

Study CLARITY AD
Symptomatic ARIA unstratified

Indication Population	Lecanemab n/N	Control n/N	RR (95% CI)	RR	95% CI
MCI + AD					
Total population	31/898	2/897		15.48	[3.72, 64.50]
Approval population	16/721	1/724		16.07	[2.14, 120.83]
Research question 1 + 2 (ACT-compliant)	13/391	1/383		12.73	[1.67, 96.87]
Not ACT-compliant	3/330	0/341		7.23	[0.38, 139.48]
MCI					
MCI population	—/—	—/—		—	—
MCI population (approval-compliant)	—/—	—/—		—	—
Research question 1 (untreated)	6/252	0/245		12.64	[0.72, 223.18]
Not ACT-compliant (with AChEI)	—/—	—/—		—	—
Not ACT-compliant (with memantine)	—/—	—/—		—	—
AD					
Mild AD population	—/—	—/—		—	—
Mild AD population (approval-compliant)	—/—	—/—		—	—
Research question 2 (with AChEI)	7/139	1/138		6.95	[0.87, 55.74]
Not ACT-compliant (untreated)	—/—	—/—		—	—
Not ACT-compliant (with memantine)	—/—	—/—		—	—

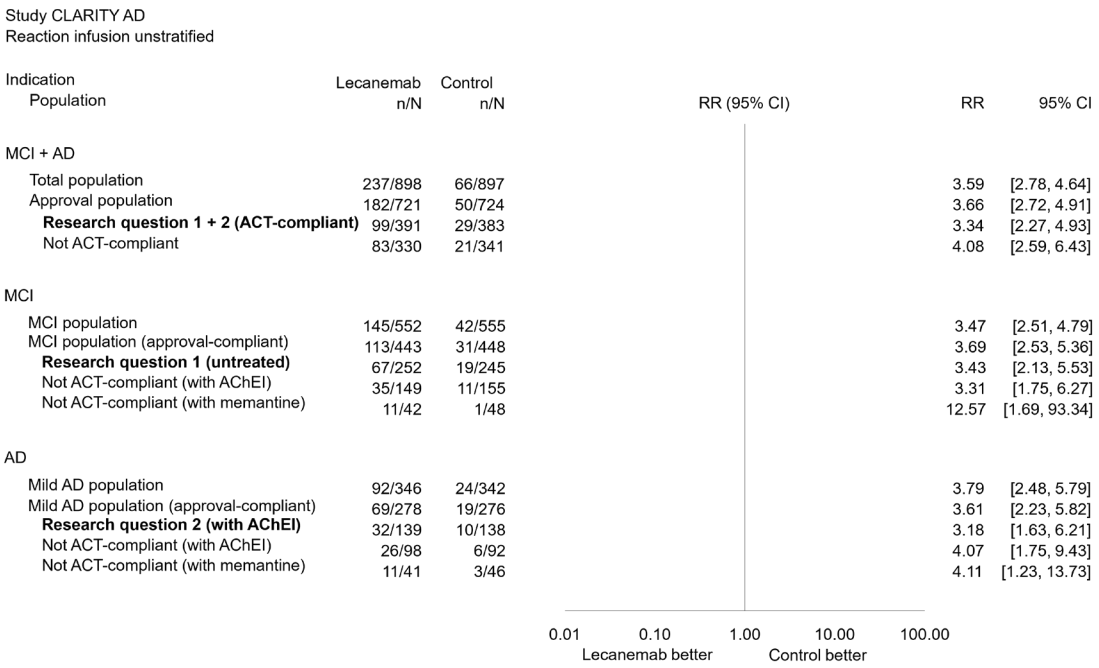


The terms approval population and approval-compliant refer to the marketing authorization of lecanemab. The term untreated refers to concomitant medication.

Institute's calculation of effect and CI (asymptotic). The results on the event rates (n/N) for 'research questions 1 + 2 (ACT-compliant)' and 'non-ACT-compliant' (first block) are based on the Institute's calculations.

AChEI: acetylcholinesterase inhibitors; ACT: appropriate comparator therapy; AD: mild Alzheimer's dementia; ARIA: amyloid-related imaging abnormalities; CI: confidence interval; MCI: mild cognitive impairment; N: number of analysed patients; n: number of patients with event; RR: relative risk

Figure 22: Forest plots for the outcome symptomatic ARIA events in the CLARITY AD study



The terms approval population and approval-compliant refer to the marketing authorization of lecanemab. The term untreated refers to concomitant medication.

Institute's calculation of effect and CI (asymptotic). The results on the event rates (n/N) for 'research questions 1 + 2 (ACT-compliant)' and 'non-ACT-compliant' (first block) are based on the Institute's calculations.

AChEI: acetylcholinesterase inhibitors; ACT: appropriate comparator therapy; AD: mild Alzheimer's dementia; CI: confidence interval; MCI: mild cognitive impairment; N: number of analysed patients; n: number of patients with event; RR: relative risk

Figure 23: Forest plots for the outcome infusion-related reaction (AE) in the CLARITY AD study

Appendix D Supplementary detailed presentation of results relating to ARIA for research questions 1 and 2

Table 25: Results (symptomatic ARIA events, dichotomous, supplementary presentation) – RCT, direct comparison: lecanemab ± AChEI vs. placebo ± AChEI (research question 1 and research question 2)

Study patient population outcome category outcome	Lecanemab ± AChEI		Placebo ± AChEI		Lecanemab ± AChEI vs. placebo ± AChEI
	N	patients with event n (%)	N	patients with event n (%)	RR [95% CI]; p-value[a]
CLARITY AD					
Research question 1					
Side effects					
Symptomatic ARIA	252	6 (2.4)	245	0 (0)	12.64 [0.72; 223.18]; 0.016
Symptomatic ARIA-E	252	4 (1.6)	245	0 (0)	8.75 [0.47; 161.68]; 0.0499
Symptomatic ARIA-H	252	2 (0.8)	245	0 (0)	4.86 [0.24; 100.75]; 0.211
Serious ARIA	252	1 (0.4)	245	0 (0)	2.92 [0.12; 71.26]; 0.515
Serious ARIA-E	252	1 (0.4)	245	0 (0)	2.92 [0.12; 71.26]; 0.515
Serious ARIA-H	252	0 (0)	245	0 (0)	NC
Asymptomatic serious ARIA	252	0 (0)	245	1 (0.4)	0.32 [0.01; 7.92]; 0.368
Research question 2					
Side effects					
Symptomatic ARIA	139	7 (5.0)	138	1 (0.7)	6.95 [0.87; 55.74]; 0.034
Symptomatic ARIA-E	139	5 (3.6)	138	0 (0)	10.92 [0.61; 195.64]; 0.025
Symptomatic ARIA-H	139	3 (2.2)	138	1 (0.7)	2.98 [0.31; 28.28]; 0.408
Serious ARIA	139	2 (1.4)	138	0 (0)	4.96 [0.24; 102.47]; 0.211
Serious ARIA-E	139	1 (0.7)	138	0 (0)	2.98 [0.12; 72.49]; 0.529
Serious ARIA-H	139	2 (1.4)	138	0 (0)	4.96 [0.24; 102.47]; 0.211
Asymptomatic serious ARIA	139	0 (0)	138	0 (0)	NC

a. Institute's calculation, unconditional exact test (CSZ method according to [6]).

AChEI: acetylcholinesterase inhibitors; ARIA: amyloid-related imaging abnormality; ARIA-E: amyloid-related imaging abnormalities-oedema/effusion; ARIA-H: amyloid-related imaging abnormalities – haemorrhage; CI: confidence interval; n: number of patients with (at least 1) event; N: number of analysed patients; NC: not calculated; RCT: randomized controlled trial; RR: relative risk

Appendix E Results on side effects

The tables below present proportions of events of the System Organ Classes (SOCs) and Preferred Terms (PTs) according to the Medical Dictionary for Regulatory Activities (MedDRA) for AEs, SAEs, each on the basis of the following criteria:

- AEs (irrespective of severity grade): events that occurred in at least 10% of patients in one study arm
- SAEs: events that occurred in at least 5% of the patients in 1 study arm
- In addition, for all events irrespective of severity grade: events that occurred in at least 10 patients and in at least 1% of patients in one study arm

For the outcome of discontinuation due to AEs, a complete presentation of all events (SOCs/PTs) that resulted in discontinuation is provided.

E.1 Research question 1

Table 26: Common AEsa – RCT, direct comparison: lecanemab vs. placebo (research question 1) (multipage table)

Study	Patients with event n (%)	
SOC[b] PT[b]	lecanemab N = 252	placebo N = 245
CLARITY AD		
Overall AE rate	226 (89.7)	208 (84.9)
Cardiac disorders	23 (9.1)	20 (8.2)
Ear and labyrinth disorders	12 (4.8)	8 (3.3)
Eye disorders	17 (6.7)	17 (6.9)
Gastrointestinal disorders	65 (25.8)	48 (19.6)
Diarrhoea	11 (4.4)	11 (4.5)
Nausea	13 (5.2)	7 (2.9)
General disorders and administration site conditions	51 (20.2)	38 (15.5)
Fatigue	12 (4.8)	9 (3.7)
Infections and infestations	93 (36.9)	81 (33.1)
COVID-19	18 (7.1)	17 (6.9)
Nasopharyngitis	12 (4.8)	7 (2.9)
Urinary tract infection	22 (8.7)	22 (9.0)
Injury, poisoning and procedural complications	110 (43.7)	71 (29.0)
Contusion	14 (5.6)	11 (4.5)
Fall	32 (12.7)	22 (9.0)
Infusion related reaction	66 (26.2)	17 (6.9)
Investigations	31 (12.3)	22 (9.0)

Table 26: Common AEsa – RCT, direct comparison: lecanemab vs. placebo (research question 1) (multipage table)

Study	Patients with event n (%)	
SOC[b] **PT[b]**	**lecanemab** **N = 252**	**placebo** **N = 245**
Metabolism and nutrition disorders	22 (8.7)	16 (6.5)
Musculoskeletal and connective tissue disorders	75 (29.8)	77 (31.4)
Arthralgia	24 (9.5)	25 (10.2)
Back pain	19 (7.5)	16 (6.5)
Pain in extremity	9 (3.6)	10 (4.1)
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	28 (11.1)	15 (6.1)
Nervous system disorders	114 (45.2)	76 (31.0)
Amyloid-related imaging abnormalities – microhaemorrhages and haemosiderin deposits	28 (11.1)	14 (5.7)
Amyloid-related imaging abnormality – oedema/effusion	28 (11.1)	3 (1.2)
Dizziness	18 (7.1)	12 (4.9)
Headache	33 (13.1)	17 (6.9)
Superficial siderosis of the central nervous system	12 (4.8)	6 (2.4)
Psychiatric disorders	41 (16.3)	40 (16.3)
Anxiety	18 (7.1)	14 (5.7)
Depression	4 (1.6)	11 (4.5)
Renal and urinary disorders	23 (9.1)	12 (4.9)
Respiratory, thoracic and mediastinal disorders	27 (10.7)	25 (10.2)
Cough	10 (4.0)	7 (2.9)
Skin and subcutaneous tissue disorders	29 (11.5)	24 (9.8)
Vascular disorders	35 (13.9)	32 (13.1)
Hypertension	15 (6.0)	14 (5.7)

a. Events that occurred in ≥ 10 patients in at least one study arm.
b. MedDRA version 25.0; SOC and PT notation adopted without modification from the supplementary submission in the context of the comments.

AE: adverse event; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with at least one event; N: number of analysed patients; ND: no data; PT: Preferred Term; RCT: randomized controlled trial; SOC: System Organ Class; vs.: versus

Table 27: Common SAEsa – RCT, direct comparison: lecanemab vs. placebo (research question 1)

Study	**Patients with event n (%)**	
SOC[b] **PT[b]**	**lecanemab** **N = 252**	**placebo** **N = 245**
CLARITY AD		
Overall SAE rate	37 (14.7)	28 (11.4)
Injury, poisoning and procedural complications	11 (4.4)	6 (2.4)

a. Events that occurred in ≥ 10 patients in at least one study arm.
b. MedDRA version 25.0; SOC and PT notation adopted without modification from the supplementary submission in the context of the comments.

MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with at least one event; N: number of analysed patients; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class

Table 28. Discontinuations due to AEs – RCT, direct comparison: lecanemab versus placebo (research question 1)

Study	Patients with event n (%)	
SOC[a] **PT[a]**	**lecanemab** **N = 252**	**placebo** **N = 245**
CLARITY AD		
Overall rate of discontinuations due to AEs	11 (4.4)	7 (2.9)
Cardiac disorders	0 (0)	1 (0.4)
Myocardial infarction	0 (0)	1 (0.4)
General disorders and administration site conditions	1 (0.4)	0 (0)
Hypothermia	1 (0.4)	0 (0)
Infections and infestations	0 (0)	2 (0.8)
COVID-19	0 (0)	1 (0.4)
Tracheobronchitis	0 (0)	1 (0.4)
Injury, poisoning and procedural complications	3 (1.2)	2 (0.8)
Infusion related reaction	3 (1.2)	0 (0)
Subdural haematoma	0 (0)	2 (0.8)
Investigations	0 (0)	1 (0.4)
Hepatic enzyme increased	0 (0)	1 (0.4)
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	2 (0.8)	0 (0)
Breast cancer	1 (0.4)	0 (0)
Prostate cancer metastatic	1 (0.4)	0 (0)
Nervous system disorders	6 (2.4)	1 (0.4)
Amyloid-related imaging abnormalities – microhaemorrhages and haemosiderin deposits	4 (1.6)	0 (0)
Amyloid-related imaging abnormality – oedema/effusion	1 (0.4)	0 (0)
Haemorrhage intracranial	0 (0)	1 (0.4)
Superficial siderosis of the central nervous system	1 (0.4)	0 (0)
Respiratory, thoracic and mediastinal disorders	1 (0.4)	0 (0)
Cough	1 (0.4)	0 (0)
Vascular disorders	0 (0)	1 (0.4)
Deep vein thrombosis	0 (0)	1 (0.4)
Venous thrombosis limb	0 (0)	1 (0.4)

a. MedDRA version 25.0; SOC and PT notation adopted without modification from the supplementary submission in the context of the comments.

AE: adverse event; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with at least one event; N: number of analysed patients; PT: Preferred Term; RCT: randomized controlled trial; SOC: System Organ Class

E.2 Research question 2

Table 29: Common AEsa – RCT, direct comparison: lecanemab + AChEI vs. placebo AChEI (research question 2)

Study	Patients with event n (%)	
SOC[b] PT[b]	lecanemab N = 139	placebo N = 138
CLARITY AD		
Overall AE rate	127 (91.4)	112 (81.2)
Cardiac disorders	13 (9.4)	5 (3.6)
Eye disorders	12 (8.6)	12 (8.7)
Gastrointestinal disorders	36 (25.9)	37 (26.8)
Diarrhoea	10 (7.2)	16 (11.6)
General disorders and administration site conditions	29 (20.9)	26 (18.8)
Infections and infestations	39 (28.1)	49 (35.5)
Urinary tract infection	5 (3.6)	17 (12.3)
Injury, poisoning and procedural complications	56 (40.3)	30 (21.7)
Fall	17 (12.2)	12 (8.7)
Infusion related reaction	32 (23.0)	10 (7.2)
Investigations	24 (17.3)	14 (10.1)
Metabolism and nutrition disorders	8 (5.8)	14 (10.1)
Musculoskeletal and connective tissue disorders	39 (28.1)	24 (17.4)
Arthralgia	12 (8.6)	3 (2.2)
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	14 (10.1)	9 (6.5)
Nervous system disorders	62 (44.6)	41 (29.7)
Amyloid-related imaging abnormalities – microhaemorrhages and haemosiderin deposits	14 (10.1)	2 (1.4)
Amyloid-related imaging abnormality – oedema/effusion	14 (10.1)	2 (1.4)
Headache	14 (10.1)	10 (7.2)
Psychiatric disorders	26 (18.7)	33 (23.9)
Anxiety	7 (5.0)	10 (7.2)
Respiratory, thoracic and mediastinal disorders	21 (15.1)	14 (10.1)
Skin and subcutaneous tissue disorders	27 (19.4)	22 (15.9)
Vascular disorders	16 (11.5)	12 (8.7)

a. Events that occurred in ≥ 10 patients in at least one study arm.
b. MedDRA version 25.0; SOC and PT notation adopted without modification from the supplementary submission in the context of the comments.

AChEI: acetylcholinesterase inhibitors; AE: adverse event; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with at least one event; N: number of analysed patients; PT: Preferred Term; RCT: randomized controlled trial; SOC: System Organ Class

Table 30: Common SAEsa – RCT, direct comparison: lecanemab + AChEI vs. placebo + AChEI (research question 2)

Study	**Patients with event n (%)**	
SOC **PT**	**lecanemab** **N = 139**	**placebo** **N = 138**
CLARITY AD		
Overall SAE rate[a]	20 (14.4)	14 (10.1)
a. For SAEs, no MedDRA SOCs and PTs met the criterion for presentation.		
AChEI: acetylcholinesterase inhibitors; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with at least one event; N: number of analysed patients; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class		

Table 31: Discontinuations due to AEs – RCT, direct comparison: lecanemab + AChEI versus placebo + AChEI (research question 2)

Study	Patients with event n (%)	
SOC[a] **PT[a]**	**lecanemab** **N = 139**	**placebo** **N = 138**
CLARITY AD		
Overall rate of discontinuations due to AEs	10 (7.2)	4 (2.9)
Blood and lymphatic system disorders	1 (0.7)	0 (0)
Thrombocytopenia	1 (0.7)	0 (0)
General disorders and administration site conditions	0 (0)	1 (0.7)
Death	0 (0)	1 (0.7)
Infections and infestations	1 (0.7)	0 (0)
COVID-19	1 (0.7)	0 (0)
Injury, poisoning and procedural complications	2 (1.4)	0 (0)
Infusion related reaction	1 (0.7)	0 (0)
Subdural haematoma	1 (0.7)	0 (0)
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	1 (0.7)	0 (0)
Liver metastasis	1 (0.7)	0 (0)
Small cell lung cancer	1 (0.7)	0 (0)
Nervous system disorders	5 (3.6)	1 (0.7)
Amyloid-related imaging abnormalities – microhaemorrhages and haemosiderin deposits	1 (0.7)	1 (0.7)
Amyloid-related imaging abnormality – oedema/effusion	2 (1.4)	0 (0)
Cerebral haemorrhage	1 (0.7)	0 (0)
Migraine	0 (0)	1 (0.7)
Motor neurone disease	1 (0.7)	0 (0)
Myasthenia gravis	1 (0.7)	0 (0)
Superficial siderosis of the central nervous system	1 (0.7)	0 (0)
Skin and subcutaneous tissue disorders	1 (0.7)	1 (0.7)
Pemphigoid	0 (0)	1 (0.7)
Urticaria	1 (0.7)	0 (0)
Vascular disorders	0 (0)	1 (0.7)
Hypertension	0 (0)	1 (0.7)

a. MedDRA version 25.0; SOC and PT notation adopted without modification from the supplementary submission in the context of the comments.

AChEI: acetylcholinesterase inhibitors; AE: adverse event; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with at least one event; N: number of analysed patients; PT: Preferred Term; RCT: randomized controlled trial; SOC: System Organ Class