Lecanemab
(early-stage Alzheimer's disease)

Benefit assessment according to §35a SGB V[1]

EXTRACT

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IQWiG thanks the medical and scientific advisor for his contribution to the dossier assessment. However, the advisor was not involved in the actual preparation of the dossier assessment. The responsibility for the contents of the dossier assessment lies solely with IQWiG.

Patient and family involvement

The questionnaire on the disease and its treatment was answered by one person.

IQWiG thanks the respondent for participating in the written exchange about how she experienced the disease and its treatment and about the treatment goals. The respondent was not involved in the actual preparation of the dossier assessment.

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Part I: Benefit assessment

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I List of abbreviations

Abbreviation	Meaning
AChEI	acetylcholinesterase inhibitor
ACT	appropriate comparator therapy
ADAS-COG14	Alzheimer's Disease Assessment Scale-Cognitive Subscale
AE	adverse event
ApoE ε4	apolipoprotein E ε4
ARIA	amyloid-related imaging abnormalities
CDR	Clinical Dementia Rating
CDR-GS	Clinical Dementia Rating Global Score
CDR-SB	Clinical Dementia Rating – Sum of Boxes
CTCAE	Common Terminology Criteria for Adverse Events
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
MCI	mild cognitive impairment
MMST	mini mental status test
MRI	magnetic resonance imaging
NIA-AA	National Institute on Aging and the Alzheimer's Association
PET	positron emission tomography
QOL AD	Quality of Life in Alzheimer's disease
RCT	randomized controlled trial
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SmPC	Summary of Product Characteristics
WMS-IV LMII	Wechsler Memory Scale-IV Logical Memory subscale II

I 1 Executive summary of the benefit assessment

Background

In accordance with § 35a Social Code Book V, the Federal Joint Committee (G-BA) has commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the drug lecanemab. The assessment is based on a dossier compiled by the pharmaceutical company (hereinafter referred to as the 'company'). The dossier was sent to IQWiG on 27 August 2025.

Research question

The aim of this report is to assess the added benefit of lecanemab compared with the appropriate comparator treatment (ACT) in adults with a clinical diagnosis of mild cognitive impairment (MCI) and mild dementia due to Alzheimer's disease (collectively referred to as early Alzheimer's disease) who are apolipoprotein E ε4 (ApoE ε4) non-carriers or heterozygotes with confirmed amyloid pathology.

The research questions presented in Table 2 were defined in accordance with the ACT specified by the G-BA.

Table 2: Research questions of the benefit assessment of lecanemab

Research question	Therapeutic indication	ACT[a]
Therapeutic indication: 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 drugs used are to be applied in accordance with the marketing authorization within the context of a study.

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

If necessary for better readability, this benefit assessment uses the following terms to refer to the patient populations (relevant to the assessment) of the research questions presented in Table 2:

- Research question 1 for patients with MCI due to Alzheimer's disease who are ApoE ε4 non-carriers or heterozygotes
- Research question 2 for patients with mild Alzheimer's dementia who are ApoE ε4 non-carriers or heterozygotes

Deviating from the G-BA's ACT, the company defined an approach of physician's choice that accompanies the course of the disease as the ACT for the two populations covered by the aforementioned research questions and across both research questions. Nevertheless, it explains why, in its opinion, the G-BA's ACT has been implemented. The company's deviating comparator therapy has no consequence regarding the completeness of the study pool, but results in inadequate data processing with regard to the research questions of the benefit assessment. The assessment of the added benefit was conducted in comparison with the G-BA's ACT presented in Table 2.

The assessment was conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. Randomized controlled trials (RCTs) with a minimum duration of 18 months were used for the derivation of the added benefit in the present therapeutic indication.

Study pool and study design

The CLARITY AD study was used for both research questions of the benefit assessment. The CLARITY AD study is a randomized, double-blind study on the comparison of lecanemab with placebo. The study included patients aged between 50 and 90 years with MCI due to Alzheimer's disease or mild Alzheimer's dementia (each according to the clinical criteria of the National Institute on Aging and the Alzheimer's Association [NIA-AA]). In addition, patients had to have a Clinical Dementia Rating (CDR) score (CDR global score, CDR-GS) of 0.5 (for a diagnosis of MCI due to Alzheimer's disease) or 0.5 to 1.0 (for a diagnosis of mild Alzheimer's dementia), as well as a score of at least 0.5 in the domain memory of the CDR at screening and baseline. There had to be positive biomarker detection of amyloid pathology in the brain. The study only included patients with a mini mental status test (MMST) score of 22 or 30. If patients were already receiving treatment for Alzheimer's disease, such as acetylcholinesterase inhibitors (AChEIs) or memantine, the dose had to have been stable for at least 12 weeks prior to baseline. Patients who had not previously received any medication for the treatment of Alzheimer's disease were also eligible for the study.

In the CLARITY AD study, a total of 1795 patients were randomly assigned in a 1:1 ratio to treatment with lecanemab (N = 898) or placebo (N = 897). It was necessary to keep the treatment for Alzheimer's disease stable throughout the study. Where medically necessary, it was permitted to adjust an existing concomitant anti-dementia therapy and to initiate anti-

dementia therapy in previously untreated patients. The treatment was scheduled to last 18 months.

Primary outcome of the study was the change in the baseline Clinical Dementia Rating – Sum of Boxes (CDR-SB) after 18 months of treatment. Patient-relevant secondary outcomes were recorded in the categories of morbidity, health-related quality of life, and side effects.

Subpopulations of the CLARITY AD study

Module 4A contains analyses of the total population of the CLARITY AD study. As the study's total population does not take into account either the restrictions of the marketing authorization (authorization criteria: no treatment for patients with homozygous ApoE ε4 carrier status or for patients using anticoagulants) or the ACT specified by the G-BA in accordance with the research questions, it is not suitable for this benefit assessment. In Module 4A, Appendix 4-G, the company also provides analyses of further subpopulations. The company first identifies the subpopulations of patients with MCI due to Alzheimer's disease or mild Alzheimer's dementia, using the diagnosis as stated in the questionnaire at the start of the study. From the subpopulations described above, the company forms further subpopulations that take into account the comparator therapy specified by the G-BA (MCI population without anti-dementia drugs and mild Alzheimer's dementia population receiving AChEI therapy; subpopulations without consideration of the marketing authorization). In Module 4A, Appendix 4-G, the company presents subgroup analyses for the subpopulations described above regarding the characteristic "ApoE ε4 carrier status according to genotype and use of anticoagulants at baseline" (non-carriers or heterozygotes not using anticoagulants at baseline vs. homozygous carriers or use of anticoagulants at baseline), which also address the regulatory requirements and thus the research questions at hand. For this benefit assessment, the following subpopulations are therefore considered and are referred to below as relevant subpopulations:

- Research question 1: 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 (MCI population compliant with the marketing authorization without anti-dementia drugs; N = 252 vs. N = 245)
- Research question 2: patients with mild Alzheimer's dementia with ongoing AChEI therapy at baseline, who are ApoE ε4 non-carriers or heterozygotes, and who were not using anticoagulants at baseline (the mild Alzheimer's dementia population in line with the marketing authorization receiving AChEI therapy; N = 139 vs. N = 138)

Research question 1 and research question 2 cover 28% and 16% respectively of the total patient population, and 41% and 23% respectively of the lecanemab approval population of the CLARITY AD study.

Due to the study design (administration of AChEIs as concomitant therapy in both study arms), this benefit assessment only allows conclusions regarding the use of lecanemab as add-on therapy to existing AChEI treatment (hereinafter referred to as lecanemab + AChEI) for patients with mild Alzheimer's dementia. Research question 2 in principle also covers the use of lecanemab as monotherapy compared with AChEIs. However, due to the lack of suitable data, no conclusions can be drawn on this matter in the present benefit assessment.

Limitations of the CLARITY AD study

The results of the study were used for the benefit assessment. However, there are the following limitations, which reduce the certainty of conclusions:

- Missing data on the use of the existing AChEI therapy: there is no information on the dosage or the time points of the AChEI therapy adjustments.
- Lack of guidelines on how to deal with a lack of efficacy or progression to the next stage:
  - If the disease progresses to the moderate stage, treatment with lecanemab should be discontinued in accordance with the Summary of Product Characteristics (SmPC). However, the study did not provide for discontinuation of treatment with lecanemab upon progression to the moderate stage. It is also unclear what proportion of patients progress to moderate Alzheimer's dementia and therefore have to discontinue treatment.
  - For both lecanemab and AChEIs, regular evaluation of cognitive functioning and clinical symptoms is also indicated. Among other things, this review is intended to help determine whether treatment should be discontinued if there is a lack of clinical efficacy. However, an overall assessment by the physicians regarding a lack of efficacy, with corresponding requirements to discontinue lecanemab or AChEIs was not planned in the course of the study. According to the study protocol, lecanemab was administered regardless of treatment response. Discontinuation of lecanemab was only planned in the event of certain side effects.

    In the study, AChEI was administered as concomitant therapy. The study protocol stipulated that existing AChEI treatment should be continued as far as possible without change. Adjustments of the therapy were to be avoided, but could be made if medically necessary. The proportion of patients who discontinued their AChEI medication that was ongoing at the start of the study during the course of the study was in 1-digit range. The company did not provide any reasons for the therapy adjustments. It is therefore unclear whether the AChEIs were discontinued due to a lack of therapeutic efficacy or whether treatment with another drug was possibly initiated.

- Initiation of anti-dementia therapy during the course of the study was permitted for previously untreated patients. In accordance with the guidelines, patients with MCI at baseline should be recommended treatment with AChEIs upon progression to the stage of mild Alzheimer's dementia. Both AChEIs and memantine are suitable treatment options for patients with mild Alzheimer's dementia at baseline who progress to the moderate stage during the course of the study. The available data on dose adjustments for patients with MCI without anti-dementia drugs (without taking into account regulatory requirements) at baseline show that treatment was initiated in 11% of patients. Of the patients with mild Alzheimer's dementia receiving AChEI therapy, 4.5% started a new medication during the course of the study. However, it is not known when or why these adjustments were made.
- It is therefore questionable for both research questions whether the study employed appropriate therapies upon progression to the next stage of the disease. Furthermore, the protocol made no specifications regarding the assessment of a lack of clinical efficacy during the course of the study.

- Lack of information on non-drug therapies: The company does not provide details on the proportion and type of non-drug therapies used during the study.

Risk of bias and certainty of conclusions (research questions 1 and 2)

The risk of bias was rated as high for the results for all outcomes except the outcome discontinuation due to adverse events (AEs).

Consideration of further aspects on the certainty of conclusions

As described above, there remain further uncertainties regarding the intervention and the implementation of the ACT. The certainty of conclusions of the study results for the given research questions was therefore reduced.

Based on the available information from the CLARITY AD study, at most hints, e.g. of an added benefit, could be derived for all outcomes presented.

Research question 1

Results

Mortality

All-cause mortality

There are no data on deaths during the course of the study for the relevant subpopulation. Based on the available data on the MCI population without anti-dementia drugs (subpopulation without consideration of the regulatory requirements), it can be estimated with sufficient certainty that no statistically significant result is to be expected in the relevant

sub-population either. 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.

Cognition (ADAS-Cog14)

There was no statistically significant difference between the treatment groups for the outcome cognition, recorded using the Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-COG14). There is no hint of an added benefit of lecanemab in comparison with watchful waiting; an added benefit is therefore not proven.

Independence in everyday life

No suitable data are available for the outcome independence in everyday life. 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 are available for the outcome of behavioural changes. 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)

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

Health-related quality of life (Quality of Life in Alzheimer's disease [QOL AD])

No statistically significant difference between treatment groups was found for the outcome health-related quality of life recorded with 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.

Side effects

SAEs and discontinuation due to AEs

No statistically significant difference between treatment groups was found for either of the outcomes of serious adverse events (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

No data are available for the relevant subpopulation regarding symptomatic ARIA events during the course of the study. There was no hint of greater or lesser harm from lecanemab in comparison with watchful waiting; an added benefit is therefore not proven. However, based on the results from other populations, a greater harm from lecanemab compared with watchful waiting cannot be ruled out.

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.

Other specific AEs

No suitable data are available for further specific AEs. There was no hint of greater or lesser harm from lecanemab in comparison with watchful waiting; greater or lesser harm is therefore not proven.

Probability and extent of added benefit, patient groups with therapeutically important added benefit[3] (research question 1)

On the basis of the results presented, the probability and extent of added benefit of the drug lecanemab in comparison with the ACT is assessed as follows:

For research question 1 of this benefit assessment, a negative effect was shown in the category non-serious/non-severe side effects, based on a specific AE (infusion-related reactions) with considerable extent.

No results are available for symptomatic ARIA events and further specific AEs. Moreover, no subgroup results are available for the relevant subpopulation. In the current data situation, it is not possible to assess the impact of these missing data on the overall assessment. In particular with regard to the lack of results on symptomatic ARIA events, the available results

[3] On the basis of the scientific data analysed, IQWiG draws conclusions on the (added) benefit or harm of an intervention for each patient-relevant outcome. Depending on the number of studies analysed, the certainty of their results, and the direction and statistical significance of treatment effects, conclusions on the probability of (added) benefit or harm are graded into 4 categories: (1) "proof", (2) "indication", (3) "hint", or (4) none of the first 3 categories applies (i.e., no data available or conclusions 1 to 3 cannot be drawn from the available data). The extent of added benefit or harm is graded into 3 categories: (1) major, (2) considerable, (3) minor (in addition, 3 further categories may apply: non-quantifiable extent of added benefit, added benefit not proven, or less benefit). For further details see [1,2].

do not rule out a greater harm. The outcomes independence in everyday life and behavioural changes were not recorded in the study.

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.

Research question 2

Results

Mortality

All-cause mortality

There are no data on deaths during the course of the study for the relevant subpopulation. Based on the available data on the population with mild Alzheimer's disease with AChEI therapy (subpopulation without consideration of the regulatory requirements), it can be estimated with sufficient certainty that no statistically significant result is to be expected in the relevant sub-population either. 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.

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.

Independence in everyday life

No suitable data are available for the outcome independence in everyday life. 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 are available for the outcome of behavioural changes. 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.

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.

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 amyloid-related imaging abnormalities (ARIA) events

There are no data on symptomatic ARIA events during the course of the study for the relevant subpopulation. There was no hint of greater or lesser harm from lecanemab + AChEI in comparison with AChEI; an added benefit is therefore not proven. However, based on the results from other populations, a greater harm from lecanemab compared with AChEI cannot be ruled out.

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.

Other specific AEs

No suitable data are available for further specific AEs. There was no hint of greater or lesser harm from lecanemab + AChEI in comparison with AChEI; greater or lesser harm is therefore not proven.

Probability and extent of added benefit, patient groups with therapeutically important added benefit (research question 2)

On the basis of the results presented, the probability and extent of added benefit of the drug lecanemab in comparison with the ACT is assessed as follows:

For research question 2 of this benefit assessment, a negative effect was shown in the category non-serious/non-severe side effects, based on a specific AE (infusion-related reactions) with considerable extent.

No results are available for symptomatic ARIA events and further specific AEs. Moreover, no subgroup results are available for the relevant subpopulation. In the current data situation, it is not possible to assess the impact of these missing data on the overall assessment. In particular with regard to the lack of results on symptomatic ARIA events, the available results do not rule out a greater harm. The outcomes independence in everyday life and behavioural changes were not recorded in the study.

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.

There are no suitable data available for comparing lecanemab as monotherapy with AChEI therapy as the ACT in patients with mild Alzheimer's dementia. There was no hint of an added benefit of lecanemab in comparison with the ACT for these patients. An added benefit is therefore not proven.

Probability and extent of added benefit – summary

Table 3 shows a summary of probability and extent of the added benefit of lecanemab.

Table 3: Lecanemab – probability and extent of added benefit

Research question	Therapeutic indication	ACT[a]	Probability and extent of added benefit
Therapeutic indication: 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]	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 AChEI: added benefit not proven (based on the results of the relevant study)[d] ▪ lecanemab monotherapy: added benefit not proven (no relevant study[e])

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 drugs used are to be applied in accordance with the marketing authorization within the context of a study.
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 approach for the derivation of an overall conclusion on added benefit is a proposal by IQWiG. The G-BA decides on the added benefit.

I 2 Research question

The aim of this report is to assess the added benefit of lecanemab compared with the ACT in adults with a clinical diagnosis of MCI and mild dementia due to Alzheimer's disease (collectively referred to as early Alzheimer's disease) who are ApoE ε4 non-carriers or heterozygotes with confirmed amyloid pathology.

The research questions presented in Table 4 were defined in accordance with the ACT specified by the G-BA.

Table 4: Research questions of the benefit assessment of lecanemab

Research question	**Therapeutic indication**	**ACT[a]**
Therapeutic indication: 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. 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 drugs used are to be applied in accordance with the marketing authorization within the context of a study.

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

If necessary for better readability, this benefit assessment uses the following terms to refer to the patient populations (relevant to the assessment) of the research questions presented in Table 4:

- Research question 1 for patients with MCI due to Alzheimer's disease who are ApoE ε4 non-carriers or heterozygotes.
- Research question 2 for patients with mild Alzheimer's dementia who are ApoE ε4 non-carriers or heterozygotes.

Deviating from the G-BA's ACT, the company defined an approach of physician's choice that accompanies the course of the disease as the ACT for the two populations covered by the aforementioned research questions and across both research questions. Nevertheless, it explains why, in its opinion, the G-BA's ACT has been implemented (for an explanation, see

the following section). The company's deviating comparator therapy has no consequence regarding the completeness of the study pool, but results in inadequate data processing with regard to the research questions of the benefit assessment (see Section I 3.2.2.1). The assessment of the added benefit was conducted in comparison with the G-BA's ACT presented in Table 4.

The assessment was conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. RCTs with a minimum duration of 18 months were used for the derivation of the added benefit in the present therapeutic indication. This minimum duration concurred with the company's inclusion criteria. Further considerations regarding the study duration are set out in Section I 3.2.3.1.

Deviating ACT and the company's research question

The company first identifies the two sub-populations in accordance with the G-BA's research questions and designates them as subpopulation a (for MCI) and b (for mild Alzheimer's dementia). As early as within the framework of its discussion of the research question, it then explains that the specified subpopulations can be formed from the CLARITY AD study dataset. From the company's point of view, it is appropriate to assess the total population of the study, as the interaction p-values for patients in the subpopulation a vs. the subpopulation b were statistically non-significant. The company states that its approach is intended to avoid an unnecessary loss of power resulting from a definition of the study population, which would make it more difficult to interpret the results. Furthermore, according to the G-BA, a division into these two subpopulations would not reflect the understanding of Alzheimer's disease as a continuum, nor would it reflect the reality of health care provision in Germany. According to the company, patients with MCI are often treated off-label with AChEIs in the reality of the German health care provision. Patients with mild Alzheimer's dementia were often not administered AChEIs. In the company's assessment, these patient populations are also covered by the therapeutic indication of lecanemab. In this therapeutic indication, the company hereinafter specifies 'an approach of physician's choice that accompanies the course of the disease' as the ACT for the two subpopulations specified by the G-BA. This approach was adequately implemented in the CLARITY AD study and ranged from watchful waiting to the use of symptomatic therapies as concomitant therapies, where this was deemed appropriate by the physician and the patient. In the company's view, its ACT – i.e. an 'approach of physician's choice that accompanies the course of the disease' – also takes into account patients whose routine care in Germany is not covered by the G-BA's ACT. The company thus identifies a suitable ACT applicable across the research questions, without listing the individual drugs it considers to be included, and bases its argument on the realities of clinical practice.

Assessment of the company's argumentation

Although Alzheimer's disease is described as a continuum [3,4], the course of which depends in particular on patient-specific factors such as the onset of the disease, educational attainment and activity levels, the stages of the disease are nevertheless regarded as distinct from one another in accordance with current guidelines and diagnostic criteria [3,5,6]. In particular, as MCI has not yet reached the level of cognitive impairment associated with dementia. For this reason, unlike patients with dementia, patients with MCI are not yet restricted in their daily functioning, according to diagnostic criteria [3,5,6]. The average duration of this stage is 3 to 7 years [7], although the prognosis for progression to the stage of mild Alzheimer's dementia varies considerably and depends on a number of factors [6,8]. Studies show that after 5 or more years, approximately 38% of patients with MCI develop Alzheimer's dementia [9,10] and that there is potentially a relevant proportion of MCI patients who never progress to the stage of mild Alzheimer's dementia [11,12]. Anti-dementia treatments such as AChEIs or memantine are not approved for patients with MCI [13-16]. As there is no evidence to support the efficacy of AChEIs and memantine in MCI, the guidelines also do not recommend pharmacological treatment with these drugs for this diagnosis [4,5]. However, in cases of mild Alzheimer's dementia, the guidelines recommend the use of AChEIs in accordance with the relevant marketing authorisation [4,5,17]. Although distinguishing between MCI and mild Alzheimer's dementia is challenging and highly individual, the patient populations therefore differ in terms of the on-label treatment options available to them.

In its approach of an ACT across the research questions, the company does not take into account the respective approved therapeutic indications for AChEIs and memantine, nor the recommendations set out in the guidelines. In its research question, it refers to the CLARITY AD study and considers not only patients with MCI due to Alzheimer's disease without anti-dementia drugs (research question 1) and patients with mild Alzheimer's dementia who were treated with AChEIs (research question 2), it also considers patients with MCI due to Alzheimer's disease who were treated off-label with AChEIs or memantine, as well as patients with mild Alzheimer's dementia who were not treated or received memantine. These additional patient populations are not covered by the G-BA's research questions. The relevance of these patient populations to the German healthcare context is unclear. There are hints showing that, particularly in cases where a diagnosis of Alzheimer's disease has been confirmed by biomarkers, AChEIs are sometimes prescribed even for MCI [18-21]. It is likely that both the difficult and highly individual distinction from mild Alzheimer's dementia and the patient's (or their relatives') desire for early treatment play a role here. In cases of mild Alzheimer's dementia, there are comprehensible reasons for not treating patients, such as a lack of efficacy, side effects, existing contraindications or the patient's request; however, the size of this group within the German health care context is unclear (in the CLARITY AD study, around one-third of patients diagnosed with mild Alzheimer's dementia did not receive AChEIs).

In summary, the guidelines clearly set out the diagnostic procedure and the recommended therapies. In routine care, it is possible to distinguish between MCI due to Alzheimer's disease and mild Alzheimer's dementia on the basis of impairment in activities of everyday life; however, this is difficult to assess objectively and depends both on factors specific to the individual patient and on the assessing physician (see also Section I 3.2.3.2). As determined by the G-BA, the assessment of the added benefit of lecanemab is conducted separately for the 2 research questions in Table 4, each in comparison with the ACT specified by the G-BA.

It is unclear whether this means that a patient population relevant to the German health care context is not represented. Consequently, the Appendix also presents results for various study populations (see I Appendix F and I Appendix G of the full dossier assessment) as supplementary information that do not, or do not fully, correspond to the research questions.

I 3 Information retrieval and study pool

The study pool for the assessment was compiled on the basis of the following information:

Sources used by the company in the dossier:

- Study list on lecanemab (status: 25 July 2025)
- Bibliographical literature search on lecanemab (last search on 25 July 2025)
- Search in trial registries/trial results databases for studies on lecanemab (last search on 25 July 2025)
- Search on the G-BA website for lecanemab (last search on 25 July 2025)

To check the completeness of the study pool:

- Search in trial registries for studies on lecanemab (last search on 08 September 2025); for search strategies, see I Appendix A of the full dossier assessment

The review did not identify any additional relevant studies of direct comparison of lecanemab versus the ACT in this therapeutic indication.

In Module 4A, the company states that, in addition to the CLARITY AD study – which is relevant to this benefit assessment – the study 201 [22] was also identified. It goes on to explain that the 201 study was not used to assess the added benefit of lecanemab. It justifies this on the grounds that the randomization scheme was compromised, leading to a significant loss of power of Study 201, as well as the low response rates at Week 79 in the intervention arm, which would strongly limit the ability to identify and interpret relevant treatment effects. The results of the 201 study would therefore not provide any new insights relevant to the CLARITY AD study. In Module 4A, Appendix 4-G of the full dossier assessment, the company presented results from study as supplementary information.

Study 201 and its unsuitability for benefit assessment are described below.

Description of the 201 study

The 201 study is a randomized, double-blind study comparing different lecanemab dosing regimens versus placebo. The study was conducted between 2012 and 2024, with the randomized phase having been completed as early as 2018. The study included patients aged between 50 and 90 years with MCI due to Alzheimer's disease, as well as patients with mild Alzheimer's dementia. Patients with MCI had to meet the clinical criteria of the NIA-AA for MCI due to Alzheimer's disease with an intermediate probability [23]. Furthermore, in accordance with the inclusion criteria, patients were required to have a CDR-GS of 0.5 and a score of at least 0.5 in the domain memory of the CDR at screening and baseline. Patients with

MCI due to Alzheimer's disease had to report a subjective decline in memory with a gradual onset and slow progression during the year prior to the start of the study, as confirmed by a reference person. Patients with mild Alzheimer's dementia had to meet the clinical NIA-AA criteria for probable Alzheimer's dementia in order to participate in the study [24]. Furthermore, in accordance with the inclusion criteria, patients with mild Alzheimer's dementia had to have a CDR-GS score of 0.5 or 1.0 and a score of at least 0.5 in the domain memory of the CDR at screening and baseline.

Regardless of the diagnosis, all patients had to demonstrate an objective impairment of episodic memory, as measured by the Wechsler Memory Scale-IV Logical Memory (subscale) II. Furthermore, there had to be a confirmed positive biomarker for amyloid pathology in the brain. Only patients with a MMST score of between 22 and 30 were eligible to take part in the study. If patients were already receiving treatment for Alzheimer's disease, the dose had to have been stable for at least 12 weeks prior to baseline. Treatment with anticoagulants was prohibited from 7 days prior to the start of the study.

A total of 856 patients were included in the 201 study. The first 196 patients were randomly assigned in a 4:2:2:2:2:2 ratio either to treatment with placebo or to one of the five lecanemab treatment arms. Patients were further randomized to the lecanemab arms based on the principle of response-adaptive randomization, whereby patients were more likely to be randomized to the intervention arm that demonstrated the highest efficacy. As part of the Voluntary Harmonisation Procedure (VHP) for clinical trials, imaging procedures suggested an increased risk of developing symptomatic amyloid-related abnormal oedema/effusions (ARIA-E) in patients with positive ApoE ε4 carrier status receiving treatment with lecanemab at a dose of 10 mg/kg body weight every two weeks. Consequently, patients with homozygous and heterozygous ApoE ε4 carrier status were no longer randomized to the intervention arm with the relevant dose of 10 mg/kg every two weeks. In addition, ApoE ε4 carriers who had already been assigned to this intervention arm had to discontinue the study if they had been receiving lecanemab for less than 6 months. Stratification factors included clinical subgroups (MCI due to Alzheimer's disease vs. mild Alzheimer's dementia), use of drugs for the treatment of Alzheimer's disease (AChEIs and/or memantine vs. none), and ApoE ε4 carrier status (ApoE ε4 carriers vs. non-carriers).

Treatment with lecanemab was not completely in compliance with the SmPC [25]. Partly differing from the specifications in the SmPC, patients were to discontinue the study at the first occurrence of the following AEs: evidence of vasogenic oedema, development of macrobleeds, 1 area of superficial siderosis, symptomatic microbleeds, severe infusion-related reactions, clinical signs of meningoencephalitis or hypersensitivity reactions with signs of tissue damage. Patients in the comparator arm received placebo to maintain blinding. It was necessary to keep the treatment for Alzheimer's disease stable throughout the study.

Where medically necessary, it was permitted to adjust an ongoing concomitant anti-dementia therapy and to initiate anti-dementia therapy in previously untreated patients in both study arms. However, these patients were censored for the analyses of efficacy outcomes. No information is available regarding the dosage and time points of adjustments to the concomitant anti-dementia therapy.

Treatment was scheduled to last for 18 months, or until the occurrence of specific AEs or unacceptable toxicity, or until treatment was discontinued at the patient's request. Patients who had discontinued treatment were required to attend a premature discontinuation visit within 7 days and to undergo a follow-up examination 3 months after intake of the last dose of the study medication. Provided that the patients did not discontinue the study at the same time, they were expected to attend every scheduled visit at which clinical surveys on outcomes of the categories morbidity and side effects were carried out in accordance with the study protocol. However, only the AEs up to the early premature discontinuation visit were taken into account for the analyses of safety outcomes. All patients who were treated with the study medication until the end of the study could enter the single-arm, open-label extension phase.

Primary outcome of the study was the change from baseline to Month 12 in the Alzheimer's Disease Composite Score (ADCOMS).

Relevance of the 201 study for the benefit assessment

The inclusion and exclusion criteria for the 201 study, as well as the specifications for concomitant anti-dementia therapy, are comparable to those of the CLARITY AD study (see also Section I 3.2.1). Based on the specifications in the SmPC, only the intervention arm with a dose of 10 mg/kg of lecanemab every two weeks would be relevant. As previously described, following an amendment to the randomization scheme, patients with homozygous and heterozygous ApoE ε4 carrier status were no longer randomized to the relevant intervention arm, and those patients with homozygous and heterozygous ApoE ε4 carrier status who had already been randomized to this arm were required to withdraw from the study. Only one follow-up visit was scheduled for these patients. This also resulted in significantly shorter follow-up periods in the intervention arm among patients who had been enrolled in the study prior to the adjustment of the randomization scheme, as well as marked differences in follow-up periods compared with the placebo arm. The median follow-up duration for the subpopulation of patients with MCI without anti-dementia treatment at baseline and who had been enrolled prior to the adjustment of the randomization scheme was 3 months in the intervention arm and 18 months in the control arm. Patients in the subpopulation with mild Alzheimer's dementia and ongoing AChEI treatment at baseline who had been included in the study prior to the adjustment of the randomization scheme were followed for a median period of 5 and 18 months, respectively. Only ApoE ε4 non-carriers were not affected by the protocol

amendment (113 patients in the lecanemab arm vs. 72 patients in the placebo arm). Furthermore, in this case too, only those sub-populations that are relevant to the G-BA's research questions should be considered, i.e. those who received the appropriate therapy in line with their diagnosis (see Table 4 and the section entitled 'Relevant subpopulations of the CLARITY AD study' in Section I 3.2.2).

Furthermore, there are relevant uncertainties that also affect the population of ApoE ε4 non-carriers. Patients with certain AEs had to discontinue the study and were excluded from further observation, apart from a follow-up visit. According to the SmPC, treatment discontinuation is not planned for the above-mentioned AEs; lecanemab was therefore not used in accordance with the marketing authorization. In addition, patients whose concomitant anti-dementia treatment had been adjusted during the study were censored for the analyses of the efficacy outcomes. No data are available on how many patients in the potentially relevant subpopulations of ApoE ε4 non-carriers were affected. However, based on the available data from other populations in the study, it is assumed that the results would be significantly biased in the potentially relevant subpopulations of ApoE ε4 non-carriers in Study 201.

For the reasons stated, Study 201 will not be considered further in this benefit assessment.

I 3.1 Studies included

The study presented in the following Table 5 was included in the benefit assessment.

Table 5: Study pool – RCT, direct comparison: lecanemab vs. the ACT

Study	Study category			Available sources		
	Study for the marketing authorization of the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)	CSR (yes/no [citation])	Registry entries[b] (yes/no [citation])	Publication (yes/no [citation])
BAN2401-G000-301 (CLARITY AD[c])	Yes	Yes	No	Yes [26,27]	Yes [28-30]	Yes [31]

a. Study sponsored by the company.
b. Citation of the trial registry entries and, if available, of the reports on study design and/or results listed in the trial registries.
c. In the tables below, the study will be referred to using this acronym.

CSR: clinical study report; G-BA: Federal Joint Committee; RCT: randomized controlled trial

Concurring with the company, the CLARITY AD study was included in the benefit assessment. Two subpopulations were considered here, which correspond to the research questions with

the associated ACT listed in Table 4, and which received on-label treatment with lecanemab (see the section 'Relevant subpopulations of the CLARITY AD study' in Section I 3.2.2). Deviating from this, the company considered the total population of the CLARITY AD study in its dossier, but provides subgroup analyses for the characteristic 'ApoE ε4 carrier status according to genotype and use of anticoagulants at baseline' (non-carriers or heterozygotes not using anticoagulants at baseline vs. homozygous carriers or use of anticoagulants at baseline) in accordance with the G-BA's research questions in Module 4A, Appendix 4-G of its dossier. The subgroup 'non-carriers or heterozygotes not using anticoagulants at baseline' is used as the relevant subpopulation for the present benefit assessment.

I 3.2 Study characteristics (aspects across research questions)

As the included CLARITY AD study was relevant for both research questions of this benefit assessment, characteristics across research questions are described below. Research question-specific characteristics for research question 1 are described in Section I 4.1, and those for research question 2 are described in Section I 5.1.

Table 6 and Table 7 describe the study used for the benefit assessment.

Table 6: Characteristics of the included study – RCT, direct comparison: lecanemab versus placebo (multipage table)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
CLARITY AD	RCT, double-blind, parallel	Patients aged ≥ 50 and ≤ 90 years with early Alzheimer's disease (MCI due to Alzheimer's disease or mild Alzheimer's dementia) ▪ according to the specific NIA-AA clinical criteria for MCI due to Alzheimer's disease with intermediate probability or for probable mild Alzheimer's dementia ▪ MCI due to Alzheimer's disease: CDR-GS of 0.5 and ≥ 0.5 in the domain memory of the CDR at screening and baseline[b] ▪ mild Alzheimer's dementia: CDR-GS of 0.5 to 1.0 and ≥ 0.5 in the domain memory of the CDR at screening and baseline ▪ objective impairment of episodic memory, indicated by at least one standard deviation below the age-adjusted mean on the WMS-IV LMII[c] ▪ MMST score ≥ 22 and ≤ 30 at screening and baseline ▪ positive biomarker for amyloid pathology in the brain[d] ▪ with or without prior treatment for Alzheimer's disease[e]	Global cohort: lecanemab (N = 898) placebo (N = 897) relevant subpopulations thereof: ▪ research question 1[f]: lecanemab (n = 252) placebo (n = 245) ▪ research question 2[g]: lecanemab + AChEI (n = 139) placebo + AChEI (n = 138) Chinese cohort[h]: lecanemab (N = 54) placebo (N = 57)	Screening: up to 60 days treatment: 18 months follow-up: 3 months[i]	235 centres in: Australia, Canada, China, France, Germany, Italy, Japan, Russia, Singapore, South Korea, Spain, Sweden, United Kingdom and USA 03/2019–08/2022[j] data cut-off: 13/09/2022[k]	Primary: CDR-SB secondary: morbidity, health-related quality of life, AEs

Table 6: Characteristics of the included study – RCT, direct comparison: lecanemab versus placebo (multipage table)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
a. Primary outcomes include information without taking into account the relevance for this benefit assessment. Secondary outcomes exclusively include information on relevant available outcomes for this benefit assessment for the CLARITY AD study. b. Patients had to report a subjective declining memory function with a gradual onset and slow progression during the year prior to the start of the study, as confirmed by a reference person. c. ≤ 15 for patients aged 50 to 64, ≤ 12 for patients aged 65 to 69, ≤ 11 for patients aged 70 to 74, ≤ 9 for patients aged 75 to 79, ≤ 7 for patients aged 80 to 90. d. Shown by: PET assessment of contrast agent uptake in the brain and/or cerebrospinal fluid analysis of total tau (t-tau)/Aβ[1-42]. e. For further details, see Table 7. f. For patients with clinically diagnosed MCI due to Alzheimer's disease who are ApoE ε4 non-carriers or heterozygotes and who were not receiving anticoagulants or anti-dementia drugs at baseline. g. Patients with clinically diagnosed mild Alzheimer's dementia who are ApoE ε4 non-carriers or heterozygotes and who were not receiving anticoagulants, but AChEI at baseline. h. The Chinese cohort comprises Chinese patients who were randomized in China, independently of the randomization of the global cohort, in order to meet Chinese regulatory requirement. The benefit assessment is based on the results of the global cohort (see the following text section); the Chinese extension cohort is no presented shown in the following tables. i. Immediately following the randomized phase, patients who had completed the 18-month treatment phase as scheduled were eligible to participate in an open-label, single-arm extension phase, in which all patients were treated with lecanemab for up to 4 years, or until lecanemab became commercially available, or until a positive benefit-risk balance for this indication could not be demonstrated. Patients who discontinued the study treatment before the end of the treatment phase, or who did not participate in the extension phase for other reasons, were followed up for 3 months after the end of treatment. j. The randomized phase of the global cohort was completed on 25 August 2022; the open-label, single-arm extension phase is still ongoing. k. Prespecified final data cut-off following completion of the RCT phase, after all randomized patients had completed the 3-month follow-up period at the end of treatment or had entered the open-label extension phase of the study. AChEI: acetylcholinesterase inhibitor; ADCOMS: Alzheimer's Disease Composite Score; AE: adverse event; ε4: apolipoprotein E ε4; CDR: Clinical Dementia Rating; CDR-GS: Clinical Dementia Rating – Global Score; CDR-SB: Clinical Dementia Rating – Sum of Boxes; MCI: mild cognitive impairment; MMST: Mini Mental Status Test; n: relevant subpopulation; N: number of randomized patients; NIA-AA: National Institute on Aging and the Alzheimer's Association; RCT: randomized controlled trial; SD: standard deviation; WMS-IV LMII: Wechsler Memory Scale-IV Logical Memory subscale II						

Table 7: Characteristics of the intervention – RCT, direct comparison: lecanemab versus placebo

Study	Intervention	Comparison
CLARITY AD	Lecanemab 10 mg/kg BW IV, every 2 weeks	Placebo IV, every 2 weeks
	Dose adjustment: ▪ not allowed ▪ interruption permitted in the event of CTCAE Grade 2 infusion reactions[a] and ARIA events	
	Disallowed pretreatment ▪ investigational therapy with a therapeutic monoclonal antibody, a protein derived from a monoclonal antibody, an immunoglobulin therapy, a vaccine or new products for the treatment of Alzheimer's disease within 6 months prior to the start of the study ▪ investigational therapies with anti-amyloid therapies (including therapies using monoclonal antibodies and therapies using β-site amyloid precursor protein cleaving enzyme [BACE] inhibitors) **allowed concomitant treatment** ▪ continuation of anti-dementia pretreatment (e.g. with AChEIs, memantine[b] or both), at a stable dose ≥ 12 weeks prior to baseline ▪ biologics at a stable dose ≥ 4 weeks prior to the start of the study ▪ anticoagulants at a stable dose ≥ 4 weeks prior to the start of the study[c] ▪ thrombolytics[d] ▪ other non-AD-targeted therapies for cognitive impairment ▪ following a previous infusion-related reaction: premedication with glucocorticoids, diphenhydramine and antihistamines prior to the infusion ▪ drugs taken as on-demand medication that may impair cognitive functioning (e.g. sedatives, benzodiazepines) up to 72 hours before cognitive tests **disallowed concomitant treatment** ▪ patients who have not received anti-dementia pretreatment should not start treatment unless it is medically necessary. ▪ immunoglobulins, monoclonal antibodies (or derivatives), systemic biological immunosuppressants and plasmapheresis: from 6 months prior to baseline ▪ systemic immunosuppressants such as azathioprine, methotrexate, mycophenolate mofetil, immunomodulatory agents and other biologics: from 3 months prior to baseline ▪ if treatment with aducanumab or other anti-amyloid therapies was initiated during the study, the study treatment had to be discontinued.	

a. In the event of infusion-related reactions of CTCAE grade ≥ 3, the study treatment had to be discontinued.
b. Memantine was not allowed in Japan.
c. Patients receiving anticoagulant therapy were not permitted to take part in CSF studies.
d. The study treatment had to be interrupted during thrombolytic therapy until the patient's medical condition had stabilized or resolved.

AChEI: acetylcholinesterase inhibitors; ARIA: amyloid-related imaging abnormalities; BW: body weight; CSF: cerebrospinal fluid; IV: intravenous; RCT: randomized controlled trial

I 3.2.1 Study description

The CLARITY AD study is a randomized, double-blind study on the comparison of lecanemab with placebo. The study included patients aged 50 to 90 years with MCI due to Alzheimer's

disease or mild Alzheimer's dementia. Patients with MCI had to meet the clinical criteria of the NIA-AA for MCI due to Alzheimer's-disease with intermediate probability [23]. In addition, patients had to have a CDR-GS of 0.5 (for a diagnosis of MCI due to Alzheimer's disease) or 0.5 to 1.0 (for a diagnosis of mild Alzheimer's dementia), as well as a score of at least 0.5 in the domain memory of the CDR at screening and baseline. Patients with MCI due to Alzheimer's disease had to report a subjective decline in memory with a gradual onset and slow progression during the year prior to the start of the study, as confirmed by a reference person. In order to participate in the study, patients with mild Alzheimer's-dementia had to meet the NIA-AA clinical criteria for probable Alzheimer's-dementia [24].

Regardless of the stage of the disease, all patients had to show objective impairment of episodic memory, as measured by the Wechsler Memory Scale-IV Logical Memory subscale II (WMS-IV LMII). Furthermore, there had to be a confirmed positive biomarker for amyloid pathology in the brain. This could be done either by positron emission tomography (PET) assessment using contrast agents or by measuring total tau/amyloid β in the cerebrospinal fluid. Patients taking anticoagulants were not permitted to take part in cerebrospinal fluid diagnosis via lumbar puncture. Only patients with an MMST score of 22 to 30 were included. All patients were required to designate a person who would also take part in the visits and clinical assessments. If patients were already receiving treatment for Alzheimer's disease, such as AChEIs or memantine, the dose had to have been stable for at least 12 weeks prior to baseline. Patients who had not previously received any medication for the treatment of Alzheimer's disease were also eligible for the study.

Patients with neurological conditions that could contribute to cognitive impairment beyond that associated with Alzheimer's disease were excluded. Patients with psychiatric diagnoses or symptoms (such as hallucinations, severe depression or delusions) that could interfere with the study implementation for the affected patients were also excluded. Patients with a score of at least 8 on the Geriatric Depression Scale or who showed suicidal behaviour were excluded from the study. Similarly, patients who had experienced a transient ischaemic attack, stroke or seizure within 12 months prior to the start of the study were not eligible to take part. The detection of clinically significant lesions on brain magnetic resonance imaging (MRI) at baseline, which pointed to a different diagnosis of dementia, as well as other significant pathological findings, also led to exclusion from the study. These findings included, for example, the following diagnoses: more than 4 microbleeds (defined as having a maximum diameter of 10 mm); a single macrobleed with a diameter of more than 10 mm; an area of superficial siderosis; signs of vasogenic oedema; signs of cerebral contusion, encephalomalacia, an aneurysm, a vascular malformation or an infectious lesion; signs of multiple lacunar infarctions or strokes involving a large vascular regions, severe small-vessel or white matter disease, space-occupying lesions or brain tumours (however, lesions diagnosed as meningiomas or arachnoid cysts with a maximum diameter of less than 1 cm did

not result in exclusion). Patients whose bleeding disorder had not been adequately optimized or whose anticoagulant therapy had not been stable for at least four weeks prior to the start of the study, as well as patients whose conditions – such as heart, respiratory, gastrointestinal or kidney diseases – had not been adequately controlled were also excluded from the study.

In the CLARITY AD study, a total of 1795 patients were randomly assigned in a 1:1 ratio to treatment with lecanemab (N = 898) or placebo (N = 897). Stratification factors were clinical subgroups (MCI due to Alzheimer's disease vs. mild Alzheimer's dementia), use of drugs for the treatment of Alzheimer's disease (AChEI alone vs. memantine alone vs. AChEI and memantine vs. none), ApoE ε4 carrier status (ApoE ε4 carriers vs. non-carriers) and geographical region (North America vs. Europe [including Australia] vs. Asia-Pacific vs. China).

Treatment with lecanemab was largely in compliance with the SmPC [16]. Following the marketing authorization and the start of the benefit assessment, the time points of MRI scans to be carried out during treatment with lecanemab were updated in consultation with the EMA and the Federal Institute for Vaccines and Biomedical Medicinal Products [32]. Accordingly, a further MRI scan must be carried out prior to the third infusion of lecanemab (see also Section I 3.2.3.3). Treatment with lecanemab should not be initiated in patients currently receiving anticoagulant therapy. According to the SmPC, cognitive functioning should be examined and clinical symptoms should be assessed approximately every 6 months during the course of treatment, in order to assess whether progression to moderate Alzheimer's dementia had occurred and/or whether the clinical course suggests that lecanemab has not demonstrated efficacy in the patient and, therefore, treatment with lecanemab should possibly be discontinued. Treatment with lecanemab is not approved for moderate Alzheimer's dementia. Discontinuation of treatment with lecanemab for the reasons stated was not provided for in the study (see also the section entitled 'Lack of guidelines on how to deal with lack of efficacy or progression to the next stage' in Section I 3.2.3.3). Patients in the comparator arm received placebo to maintain blinding. The plan was to maintain the concomitant anti-dementia therapy at a stable level for at least 12 weeks prior to the start of the study and throughout the study. Where medically necessary, it was permitted to adjust an ongoing concomitant anti-dementia therapy and to initiate anti-dementia therapy in previously untreated patients in both study arms. No information is available regarding the dosage and time points of adjustments to the concomitant anti-dementia therapy (see Section I 3.2.3.3).

The treatment was scheduled to last 18 months (79 weeks). In addition to the patient's request, the following events led to treatment discontinuation: radiographically moderate or severe ARIA-E, isolated macrobleeds (> 10 mm), multiple (> 10) cumulative cerebral microbleeds, symptomatic cerebral microbleeds or symptomatic superficial siderosis, each associated with abnormal amyloid-related microbleeds and haemosiderin deposition

(ARIA-H), severe infusion-related reactions (Common Terminology Criteria for Adverse Events [CTCAE] ≥ grade 3), meningoencephalitis or hypersensitivity reactions with tissue damage. Patients who had discontinued treatment were required to attend a premature discontinuation visit within 7 days and to undergo a follow-up examination 3 months after intake of the last dose of the study medication. Provided that the patients did not discontinue the study at the same time, they were expected to attend every scheduled visit at which clinical surveys on outcomes of the categories morbidity and side effects were carried out in accordance with the study protocol. All patients who were treated with the study medication until the end of the study could switch to the single-arm, open-label extension phase.

Primary outcome of the study was the change in the baseline CDR-SB after 18 months of treatment. Patient-relevant secondary outcomes were recorded in the categories of morbidity, health-related quality of life, and side effects.

Relevance of the cohorts of the CLARITY AD study

The company exclusively used the data of the global cohort of the CLARITY AD study for its benefit assessment. It did not consider the results of the Chinese cohort and justified this with the comparatively small patient population compared to the global cohort of the study and the lack of transferability of the results to the German health care context. It also points out that the results from the Chinese cohort were recorded and analysed separately from those of the global cohort, and that a separate statistical analysis plan and clinical study report are available. According to the company, the randomization of the Chinese cohort took place much later due to significant restrictions caused by COVID-19 and was only completed one year after the randomization of the global cohort. It goes on to explain that outside China, the results of the Chinese cohort were not taken into account in the marketing authorization process – particularly by the EMA and the Food and Drug Administration (FDA). The company also highlights the high proportion of significant protocol deviations in the Chinese cohort. In 40.5% of patients in the Chinese cohort, there were significant deviations from the protocol during the conduct of the study, with 34.2% of these patients documented as having missed at least four consecutive study visits due to COVID-19. In the global cohort of CLARITY AD, missed study visits related to COVID-19 occurred in only 5.4% of patients. The company did not present the data of the Chinese cohort separately in Module 4 A, but submitted a corresponding CSR at the date of the study end on 07 July 2023.

The two cohorts of the CLARITY AD study were conducted under an identical study protocol. The only exception was a separate statistical analysis plan for the Chinese cohort. Thus, both cohorts should be considered as 1 study and the results for the entire study population should generally be used as the basis for the benefit assessment. However, the 111 patients in the Chinese cohort of the CLARITY AD study only account for around 6% of the total study population. It remains unclear how many patients would have to be assigned to research

question 1 or research question 2. Furthermore, the interpretability of the data is unclear due to the high proportion of significant protocol deviations associated with at least four consecutive missed study visits. However, it is assumed that not taking into account these additional Chinese patients does not have a relevant impact on the results. Thus, the relevant subpopulations of the global cohort were used for the benefit assessment as sufficient approximation to the relevant subpopulations of the entire study. Hereinafter, all data on the CLARITY AD study refer to the global cohort of the CLARITY AD study.

I 3.2.2 Subpopulations of the CLARITY AD study

Total study population not suitable

As previously described, the company presents analyses of the total population of the CLARITY AD study in Module 4A. These analyses do not take into account the restrictions imposed by the EMA on the marketing authorization. The proportion of patients with homozygous ApoE ε4 carrier status who were using anticoagulants at baseline in the total population was 19.6% (see also Appendix B of the full dossier assessment). In Appendix 4-G of the full dossier assessment, the company presented analyses for patients who are ApoE ε4 non-carriers or heterozygotes and who were not taking anticoagulants at baseline as part of the subgroup analyses for the characteristic 'ApoE ε4 carrier status according to genotype and use of anticoagulants at baseline' in Module 4A, Appendix 4-G.

As the total study population does not take into account either the restrictions of the marketing authorization or the ACT specified by the G-BA in accordance with the research questions (see Table 4), it is not suitable for the present benefit assessment.

Other subpopulations submitted by the company not suitable

The subpopulation of patients analysed in the subgroup analyses for the total population – comprising ApoE ε4 non-carriers or heterozygotes who were not taking anticoagulants at baseline (hereinafter referred to as the lecanemab approval population) – considers the requirements for the market authorization of lecanemab, but not the research questions defined by the G-BA. Therefore, this population is also unsuitable for this benefit assessment.

In Module 4A, Appendix 4-G, the company also provides analyses of further subpopulations. These are described below. A flowchart illustrating the formation of the subpopulations is shown in I Appendix B.1. of the full dossier assessment.

The company first identifies the subpopulations of patients with MCI due to Alzheimer's disease (hereinafter referred to as MCI population) or mild Alzheimer's dementia (hereinafter referred to as the mild Alzheimer's disease population), using the diagnosis as stated in the case report form at baseline. It is unclear to what extent, at the start of the study, a review

was carried out of any diagnosis made some time previously and of the current treatment (see also Sections I 4.1.1 and I 5.1.1).

The analyses do not take into account the EMA's restriction on the marketing authorization of lecanemab. Furthermore, in these subpopulations, concomitant therapy – i.e. the requirements of the G-BA's ACT and the respective approved therapeutic indications – is not taken into account. The MCI population includes both patients without any concomitant treatment at baseline and patients who were receiving off-label therapy with AChEIs and/or memantine at baseline. Patients in the subpopulation with mild Alzheimer's dementia (mild Alzheimer's dementia population) were receiving concomitant treatment with an AChEI and/or off-label treatment with memantine or no concomitant treatment, at baseline. 44% of patients diagnosed with MCI were received AChEI or memantine (see also I Appendix B of the full dossier assessment). The company did not explain the reasons. Furthermore, around one-third of patients in the CLARITY AD study diagnosed with mild Alzheimer's dementia did not receive an AChEI. No reasons have been given. Neither of these subpopulations therefore considers the restrictions on the market authorization of lecanemab or the specifications of the G-BA's ACT. Therefore, these populations are not suitable for this benefit assessment.

From the subpopulations described above, the company formed further subpopulations that take into account the ACT specified by the G-BA (see Table 4). To this end, it analyses the patients in the MCI population who were not receiving anti-dementia treatment at baseline, thereby identifying the MCI cohort not taking anti-dementia medication (without taking the regulatory requirements into account). For the subpopulation of patients with mild Alzheimer's dementia (the mild Alzheimer's dementia population, disregarding the regulatory requirements), it considered only patients with AChEI treatment at baseline, thereby yielding the mild Alzheimer's dementia population with AChEI therapy (disregarding the regulatory requirements). In doing so, it takes into account the drugs authorized in the relevant therapeutic indication and designated as ACT within these subpopulations. However, the restrictions set out in the marketing authorization for lecanemab are not taken into account. The proportion of patients with homozygous ApoE ε4 carrier status and use of anticoagulants at baseline was 20.4% in the MCI population without anti-dementia drugs and 18.8% in the mild Alzheimer's dementia population receiving AChEI therapy (subpopulations without consideration of regulatory requirements). These populations are not suitable for the present benefit assessment, as the ApoE ε4 carrier status represents a potentially relevant effect modifier (there are indications of a tendency towards smaller benefits and, in particular, greater disadvantages in the side effects in homozygous ApoE ε4 carriers). In this case, the question of whether at least 80% of the patients included meet the criterion (suitable population) is of secondary importance. However, where no suitable data are available for the subpopulations relevant to the assessment and where this is necessary for the interpretation

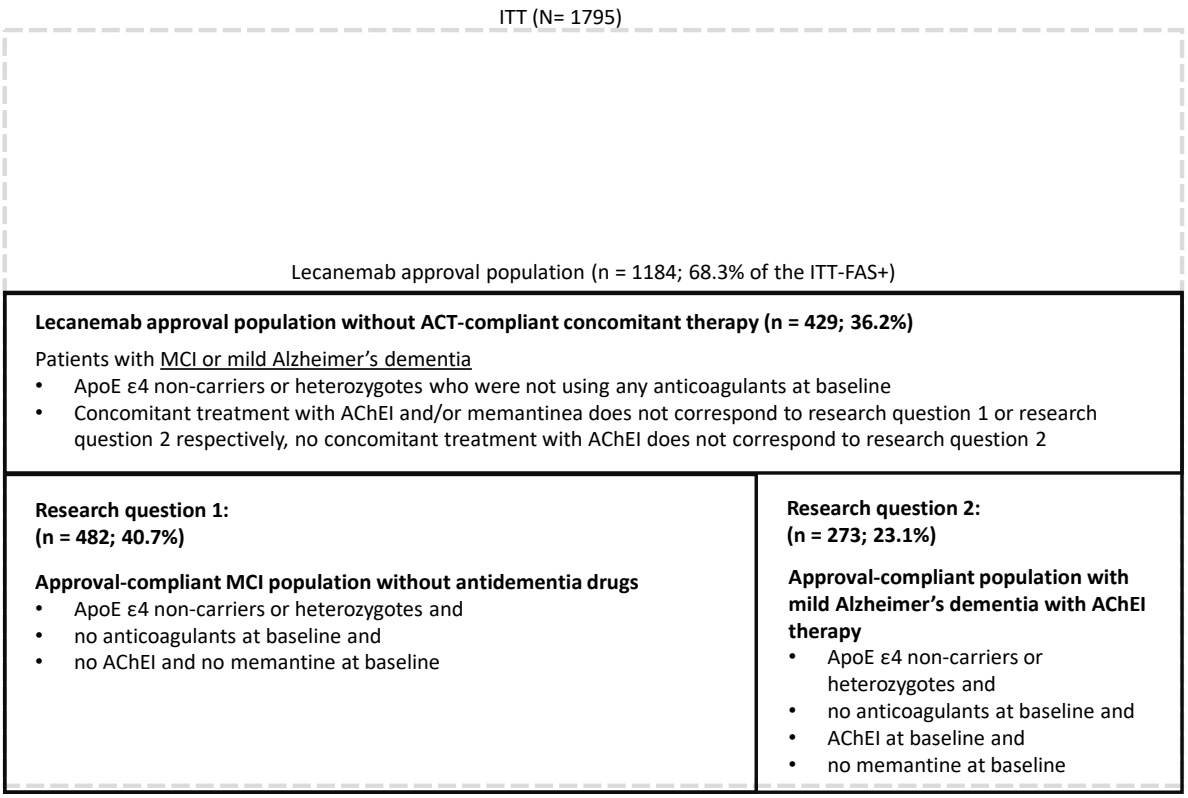
of the results, the available data and results for these two populations will nevertheless be used as supplementary information.

Relevant subpopulations of the CLARITY AD study

In Module 4A, Appendix 4-G, the company presents subgroup analyses for the subpopulations most recently described (MCI population without anti-dementia drugs and mild Alzheimer's dementia population receiving AChEI therapy [subpopulations without consideration of regulatory requirements]) regarding the characteristic 'ApoE ε4 carrier status according to genotype and use of anticoagulants at baseline' (non-carriers or heterozygotes not using anticoagulants at baseline vs. homozygous carriers or use of anticoagulants at baseline). The subgroup 'non-carriers or heterozygotes not taking anticoagulants at baseline' takes into account the restrictions imposed by the marketing authorization for lecanemab. These subgroups therefore consider both the G-BA's research questions and the respective specified ACT as well as the approved therapeutic indications of lecanemab and the comparator therapies. For this benefit assessment, the following subpopulations are therefore considered and are referred to below as relevant subpopulations:

- Research question 1: 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 (MCI population compliant with the marketing authorization without anti-dementia drugs)
- Research question 2: patients with mild Alzheimer's dementia with ongoing AChEI therapy at baseline, who are ApoE ε4 non-carriers or heterozygotes, and who were not using anticoagulants at baseline (the mild Alzheimer's dementia population in line with the marketing authorization receiving AChEI therapy)

The relevant subpopulations described above represent a significant subset of the total study population. Research question 1 and research question 2 cover 28% and 16% of the total population as well as 41% and 23% of the lecanemab approval population in the CLARITY AD study (see Figure 1).



a. In the lecanemab approval population without ACT-compliant concomitant therapy, approximately 22% of patients with MCI due to Alzheimer's disease and approximately 34% of patients with mild Alzheimer's dementia received off-label memantine.

AChEI: acetylcholinesterase inhibitors; 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 approval-compliant lecanemab subpopulations of the CLARITY AD study

In addition to the results for the relevant populations relating to research question 1 and research question 2, the pooled results for the populations of both research questions are supplementarily considered. This pooled population represents the largest possible population, taking into account the specifications of the marketing authorization and the ACT. In addition, as already mentioned in the discussion of the research questions (see Chapter I 2), the appendix also presents results for various study populations (see I Appendix F and I Appendix G of the full dossier assessment) that do not, or do not fully, correspond to the research questions.

It should also be noted that, in accordance with the marketing authorization, lecanemab may be used as monotherapy and also in combination with other anti-dementia therapies. With regard to the pretreated patient group relevant to research question 2, the CLARITY AD study only included patients who had been receiving stable AChEI therapy for at least 12 weeks, and

this therapy was continued unchanged in the course of the study. Due to the study design, this benefit assessment only allows conclusions regarding the use of lecanemab as add-on therapy to existing AChEI treatment (hereinafter referred to as lecanemab + AChEI) for patients with mild Alzheimer's dementia. However, research question 2 also covers the use of lecanemab as monotherapy compared with AChEIs. However, due to the lack of suitable data, no conclusions can be drawn on this matter in the present benefit assessment.

I 3.2.2.1 Incomplete information on the relevant sub-populations

In Module 4A, the company primarily presents the results for the total population of the CLARITY AD study. Information on the relevant subpopulations, as defined by the G-BA's research questions, is provided solely in subgroup analyses based 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 vs. homozygous carriers or use of anticoagulants at baseline). However, the available information on the relevant subpopulations was incomplete. An overview of the missing data can be found in Table 8.

Table 8: Data available for the relevant subpopulations in the CLARITY AD study – RCT, direct comparison: lecanemab vs. appropriate comparator therapy

Topic	Data situation of the relevant subpopulations[a]
Characteristics of the relevant subpopulation	ND[b]
Information on the course of the study	ND
Outcomes	
Mortality	
All-cause mortality	ND; however, conclusions can be drawn from the MCI population not receiving anti-dementia medication or the mild Alzheimer's dementia population receiving AChEI therapy (subpopulations without consideration of regulatory requirements)
Morbidity and health-related quality of life	Results from the subgroup analyses are available ND available regarding follow-up duration and questionnaire response rates
Side effects	
Symptomatic ARIA events	ND[c]
Other specific AEs	Incomplete data from the subgroup analyses[c]
Subgroup analyses	ND

a. Research question 1: 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.
Research question 2: patients with mild Alzheimer's dementia with ongoing AChEI therapy at baseline, who are ApoE ε4 non-carriers or heterozygotes, and who were not using anticoagulants at baseline.
b. Individual data on values at the time of randomization can be derived from the data on the study results (see Table 9 and Table 16).
c. See Section I 4.2.1 for a rationale.

AChEI: acetylcholinesterase inhibitor; ApoE ε4: apolipoprotein E ε4; MCI: mild cognitive impairment; ND: no data; RTC: randomized controlled trial

The dossier did not contain any information on patient characteristics, study course (treatment duration and observation periods of patients), observation periods and responses to the patient-reported outcomes questionnaires, symptomatic ARIA, further specific AEs or subgroup analyses for the subpopulations relevant to the assessment. Information on other subpopulations is provided as supplementary information in I Appendix C, I Appendix F and I Appendix G of the full dossier assessment and is taken into account in the interpretation where possible and appropriate.

I 3.2.3 Limitations of the CLARITY AD study

The results of the study were used for the benefit assessment. However, there were limitations, which are described below.

I 3.2.3.1 Duration of study with limited informative value

According to the EMA guideline on the conduct of clinical trials of drugs for the treatment of Alzheimer's disease, the study duration in this therapeutic indication should be adapted to the expected progression rate and the expected efficacy of the investigational substance [33]. A study duration of at least 18 months is specified in the early stage of Alzheimer's disease, although longer studies may be necessary in some cases. The FDA guideline for this therapeutic indication, however, recommends a follow-up period of at least two years [34]. As early Alzheimer's disease is a condition whose progression spans several years, longer-term studies are necessary, particularly in the case of MCI, in order to adequately investigate further relevant outcomes, such as the loss of independence in everyday life.

In the CLARITY AD study, patients were treated for 18 months and then followed up for a further 3 months, unless they entered the open-label extension phase. In this therapeutic indication, 18 months is accepted as the minimum duration. Nevertheless, given that this is a progressive disease which tends to progress rather slowly, particularly in its early stages, longer follow-up periods would be desirable. The company has chosen not to present the data from the extension phase of the CLARITY AD study in Module 4A, nor to compare them with data on long-term course under the ACT.

I 3.2.3.2 Uncertainties regarding the population

Uncertainties regarding the distinction between MCI and mild Alzheimer's dementia in the study versus practice in routine care

To be eligible for the CLARITY AD study, patients had to have been diagnosed with MCI due to Alzheimer's disease or mild Alzheimer's dementia based on the NIA-AA criteria. In addition, inclusion criteria were defined on the basis of the CDR-GS and MMST scores. For MCI, there was an additional requirement that patients had to report a subjective declining memory function with a gradual onset and slow progression during the year prior to the start of the

study, as confirmed by a reference person. In addition, amyloid pathology had to be confirmed by PET or cerebrospinal fluid diagnosis (see Section I 3.2.1). This assessment assumes that the company has defined the subpopulations on the basis of the relevant information provided by the investigator regarding the diagnosis (MCI due to Alzheimer’s disease or mild Alzheimer’s dementia) in the CRF.

In the German health care context, diagnosis according to the S3 guideline has so far mainly been based on a clinical investigation, short cognitive tests (such as MMSE and Montreal Cognitive Assessment [MoCA]) and detailed neuropsychological tests (such as Consortium to Establish a Registry for Alzheimer's Disease [CERAD-plus] and ADAS-Cog14) [5,6]. In addition, other causes of cognitive impairment must be ruled out, for example through blood tests or MRI scans. Distinguishing between MCI and mild Alzheimer’s dementia is challenging, as the boundaries between the two are blurred and the ability to cope with everyday life is a key distinguishing factor. The assessment depends heavily on individual factors such as educational attainment, age and the extent of abilities prior to the onset of the condition, as well as on any comorbidities. Research suggests that a neuropsychological assessment, blood tests and MRI scans are almost always carried out [20,21]. In accordance with the requirements for the marketing authorization of lecanemab, amyloid pathology will also need to be routinely assessed using a suitable method in the future; however, it is unclear to what extent blood tests might be suitable in the future in addition to the methods used in the approval study (PET or cerebrospinal fluid analysis) [5].

There is some uncertainty as to the extent to which the approach taken in the CLARITY AD study for diagnosing MCI or mild Alzheimer’s dementia, and the distinction drawn between these diagnoses, corresponds to the guidelines followed in everyday clinical practice in Germany; for example, it is unclear what role brief cognitive tests such as the MMST played in the diagnostic process within the study. Furthermore, it is unclear to what extent any previous diagnoses – even those made some time ago – and the current treatment were reviewed at the start of the study (see also Sections I 4.1.1 and I 5.1.1). The date of diagnosis was recorded in the CRF. If the diagnosis was made some time ago, the procedure followed at the time is unknown.

Overall, the resulting uncertainty is not considered to be serious enough to compromise the reliability of the certainty of conclusions.

Biomarker detection for the diagnosis of Alzheimer's disease limited to amyloid β

According to the S3-guideline, a diagnosis of MCI or dementia due to Alzheimer’s disease can only be made with high probability if there is evidence of biomarkers for amyloid β and tau pathology [5]. This is intended to serve for the differential diagnosis, as dementia and MCI can also occur in conjunction with other diseases without being associated with Alzheimer’s

disease. Irrespective of this, it is unclear whether biomarkers for amyloid and tau pathology are currently determined as standard practice in the everyday diagnosis of Alzheimer's disease. Surveys of general practitioners and clinics in Germany suggest that, when weighing up the benefits and harms to the patient, this examination may only be carried out if it is necessary for the therapy decision [20,21,35]. The testing study ENABLE on the use of PET in mild dementia [36], which investigates the benefits of amyloid PET in everyday health care for Alzheimer's dementia in Germany (explicitly excluding patients with MCI), has not yet been completed.

Intermediate probability of Alzheimer's disease can be assumed if a positive biomarker result is present only for amyloid β pathology or for neuronal damage (e.g. based on tau pathology or structural MRI) while the status of the other biomarker is unknown [3,23].

The only requirement for study inclusion was proof of amyloid pathology, as determined by PET with contrast agents or by measuring total tau and amyloid β in the cerebrospinal fluid. According to the 2011 NIA-AA criteria used in the study for the diagnosis of MCI and mild Alzheimer's dementia, this is sufficient to show intermediate probability of Alzheimer's disease. In the total population, 86% of patients had a positive amyloid PET scan (cut-off centiloid ≥ 30) at baseline, and 29% had a positive amyloid status based on cerebrospinal fluid analysis. No information was available for the relevant subpopulations. The available data show that tau pathology was assessed for some of the patients at baseline and also during the course of the study. However, the dossier provides no information on this matter. As tau pathology is an important biomarker for diagnosing the disease, corresponding information would be required. It therefore remains unclear to what extent a diagnosis made using PET with contrast agents or by measuring total tau and amyloid β in cerebrospinal fluid complies with the guidelines.

The resulting uncertainty is not considered to be serious enough to compromise the reliability of the certainty of conclusions.

Limited patient population with regard to the MMST and the psychopathological symptoms of the disease

According to the study's inclusion criteria, patients had to achieve a score of between 22 and 30 in the MMST. Low scores are associated with more severe cognitive impairment [37]; a score of 30, the maximum possible, points to no cognitive impairment. The S3 guideline sets out exploratory thresholds for classifying the severity of dementia, with a score of 20 to 26 suggesting mild dementia [5]. These figures should always be considered in the context of the specific symptoms of the disease, taking particular account of the person's literacy and age. Based on the inclusion criteria, patients with an MMST score of 20 or 21 would therefore not be eligible for the study, even though they could certainly be classified as having mild

dementia based solely on the exploratory threshold value. By contrast, patients with an MMST score of 30 – who, according to the thresholds, had no cognitive impairments – were eligible for the study.

Another aspect is the psychological and behavioural symptoms that occur in the vast majority of people affected as dementia progresses. These include, for example, depression, anxiety and apathy, as well as aggression, psychotic symptoms, disinhibited behaviour or sleep disorders [5]. Patients with any psychiatric diagnosis or symptoms (e.g. hallucinations, severe depression or delusions) that might interfere with the conduct of the study were excluded from taking part. Patients with a score of ≥ 8 on the Geriatric Depression Scale were also excluded from participation in the study. With a maximum score of 15, where a higher score indicates more severe symptoms, a score of 8 corresponds to mild to moderate depressive symptoms [38]. No further surveys using this tool were planned during the course of the study. In addition, patients with suicidal thoughts or suicidal behaviour were excluded from the study.

The psychopathology symptoms of the disease are significant in this therapeutic indication. However, the limitations on the population resulting from the inclusion and exclusion criteria (regarding depression, suicidal tendencies and the MMST) are not considered relevant in the current data situation. The aspects mentioned therefore have no consequences for the benefit assessment. Regardless of this, a comprehensive assessment would require corresponding data on patient characteristics for the subpopulations of interest. These are not available in the dossier.

The resulting uncertainty is not considered to be serious enough to compromise the reliability of the certainty of conclusions.

I 3.2.3.3 Uncertainties regarding intervention and concomitant therapy

Lack of information regarding the use of AChEI therapy

In accordance with the study protocol, any existing antidementia treatment for Alzheimer's disease, where administered, must have been stable for at least 12 days prior to the start of the study. Patients without antidementia treatment could also participate in the study. Furthermore, antidementia treatment or non-treatment was to be kept stable throughout the study. In both study arms, the adjustment of existing concomitant antidementia therapy, and the initiation of antidementia therapy in previously untreated patients was permitted if medically necessary (see also Table 7).

In the dossier, the company shall provide details regarding concomitant drug treatments at baseline and throughout the course of the study. Furthermore, in Module 4A, Appendix 4-G, it presents data, amongst other things, for the MCI population without anti-dementia

medication and the mild Alzheimer's dementia population with AChEI therapy, thereby taking into account the requirements regarding concomitant therapy in line with the research question. However, information regarding dosages or timing of AChEI adjustments are not available. However, this information would be necessary in order to check the administration of the drugs of the ACT according to the SmPC. According to the relevant SmPC, AChEIs should be titrated to the maximum tolerated dose over a defined period, taking into account clinical response and tolerability [14-16]. Clinical response should also be monitored as treatment continues. Discontinuation of treatment should be considered if no therapeutic effect is evident. Fundamentally, treatment with AChEIs should be initiated and monitored by a doctor with experience in the diagnosis and treatment of Alzheimer's disease. Information regarding aspects of concomitant anti-dementia therapy specific to each research question are described in the relevant sections for research question 1 in I 4.1.1 and for research question 2 in I 5.1.1. The data in Table 22 and Table 25 in I Appendix C of the full dossier assessment show that there are hardly any differences between the study arms, either in terms of the drugs used or in the rate of treatment adjustments. There were no signs that the AChEIs were not used in accordance with the SmPC in the population relevant to the assessment (research question 2). However, the relevant data required for verification are missing. The consequential uncertainty is taken into account in the certainty of conclusions of the results (see Section I 4.2.2).

Lack of specifications on how to deal with a lack of efficacy or progression to the next stage

According to the SmPC, lecanemab is approved for the treatment of early-stage Alzheimer's disease. If the disease progresses to the moderate stage, treatment with lecanemab should be discontinued [25]. Discontinuation of treatment with lecanemab in case of progression to the moderate stage was not planned for in the study. If continued treatment with lecanemab were to occur in the moderate stage, this would constitute off-label use. The study did not include an overall assessment by the doctors regarding progression or the transition to moderate Alzheimer's dementia. In Module 4A, the company provides analyses for the CDR-GS on confirmed deterioration, which are to depict the transition to the next disease stage in accordance with the study design. However, it has not been demonstrated to what extent these analyses are suitable for reflecting relevant disease progression. These analyses are therefore not used in this benefit assessment (see also Section I 4.2.1). The proportion of patients with progression to moderate Alzheimer's dementia and thus an indication for discontinuation was therefore unclear.

Regular evaluation of cognitive functioning and clinical symptoms is indicated for both lecanemab and AChEIs [14-16,25]. Among other things, this review is intended to help determine whether treatment should be discontinued if there is a lack of clinical efficacy. The study was designed to record therapeutic effects (see Section I 4.2.1), but did not include an

overall assessment by the physicians regarding a lack of efficacy, with corresponding specifications for the discontinuation of lecanemab or AChEIs. According to the study protocol, lecanemab was administered regardless of treatment response. Discontinuation of lecanemab was only planned in the event of certain side effects. The study protocol stipulated that existing AChEI treatment should be continued as far as possible without change. Modifications to the therapy were to be avoided, but could be made if medically necessary. In the subgroup of patients with mild Alzheimer's dementia and AChEI therapy, 3% in the lecanemab arm and 7% in the placebo arm discontinued their baseline medication (see Table 25 in I Appendix C.2 of the full dossier assessment). No information was available for the relevant subpopulations. Nor did the company provide the reasons for the therapy adjustments. It is therefore unclear whether the AChEIs were discontinued due to a lack of therapeutic efficacy or whether treatment with another drug was possibly initiated.

AChEIs are approved for the treatment of mild and moderate Alzheimer's dementia [14-16]. According to the guidelines, patients with MCI at baseline should have been recommended treatment with AChEIs at the transition to the mild dementia stage [5]. For patients with mild Alzheimer's dementia at baseline who progressed to the moderate stage during the course of the study, both AChEIs and memantine would be suitable treatment options [5]. There was no information on dose adjustments for the relevant subpopulation. Of the patients with mild Alzheimer's dementia receiving AChEI therapy, 4.5% started a new medication during the course of the study (see Table 25). There are no grounds for this.

For patients who had not been using this medication at baseline it should not be initiated during the course of the study, unless medically necessary. The available data show that 11% of the patients with MCI without anti-dementia drugs at baseline initiated such medication during the course of the study (see Table 22 in I Appendix C.1 of the full dossier assessment). No information is available regarding the relevant subpopulation or as to why the concomitant therapy was adjusted.

It is therefore unclear, in relation to both research questions, whether the treatments were discontinued in accordance with the SmPC in the event of a lack of effectiveness, and whether appropriate therapies were initiated upon progression to the next disease stage. The described uncertainties were taken into account for the assessment of the certainty of conclusions (see Section I 4.2.2).

Administration of memantine and anticoagulants during the course of the study

As described before, the use of anticoagulants or memantine was not disallowed in the study. In addition to the aspects mentioned above, the study documents show that a small proportion of patients initiated treatment with memantine or anticoagulants after the start of the study. It remains unclear whether the initiation of memantine therapy was an

appropriate treatment upon progression to the stage of moderate Alzheimer's dementia or whether it was off-label use at an earlier stage. However, based on the available data, it is assumed that the proportion of patients receiving memantine therapy during the course of the study is negligible in the subpopulations relevant to the assessment (see also Table 22 and Table 25).

Anticoagulant therapy is contraindicated during treatment with lecanemab. No data are available on the number of patients who started treatment with anticoagulants during the study. However, based on the information in the CSR regarding concomitant medication, this is also assumed to be a negligible proportion. The uncertainty regarding the administration of memantine and anticoagulants during the course of the study is not considered to be so serious as to compromise the certainty of conclusions.

Lack of information on non-drug therapies

In accordance with the current S3 guideline, non-drug therapies such as cognitive training, cognitive stimulation or physical exercise are also recommended for both of these patient groups [5]. It should also be noted that with regard to the ACT, non-drug measures as outlined in the German Remedies Directive or the catalogue of remedies (occupational therapy, e.g. cognitive training) were to be offered and documented in both study arms. As already described, since antidementia treatments such as AChEIs or memantine are not approved or recommended for patients with MCI, non-drug treatments are of particular importance for these patients. Patients with mild Alzheimer's dementia might, however, also benefit from these. Non-drug treatments were permitted during the study, but were not offered as part of the study. It was assumed that they were used, provided they were medically indicated and available. The company has not provided details on the proportion and type of non-drug therapies used during the study, although the study protocol stipulated that this information was to be recorded. The resulting uncertainty regarding the implementation of the ACT and its transferability to the German health care context is taken into account in the certainty of the results (see Section I 4.2.2).

No MRI scan is scheduled prior to the third infusion

Following marketing authorization and the start of the benefit assessment, the time points of MRI scans to be performed during treatment with lecanemab were updated in consultation with the EMA and the Federal Institute for Vaccines and Biomedical Medicinal Products [32]. Accordingly, a further MRI scan should be carried out before the third lecanemab infusion. This additional examination was introduced to enable the earlier detection of cases of amyloid-related imaging abnormalities (ARIA) and to prevent serious and fatal ARIA. These usually occur early in the course of treatment [39]. According to the SmPC, certain ARIA require an interruption or even a discontinuation of the treatment [25]. ARIA typically presents asymptomatically, but may be associated with symptoms such as headaches,

dizziness and visual impairment [40,41] (see also Section I 4.2.1). The study provided for MRI scans following the 5th, 7th and 14th infusions, as well as for ARIA follow-up. As the study did not include an MRI scan prior to the third infusion, ARIA may have been undetected, or may only have been detected later in the course of treatment although interruption or discontinuation would have been necessary. Furthermore, symptoms such as headaches or dizziness that occurred early in the course of treatment were potentially not recorded as symptomatic ARIA.

The resulting uncertainty is not considered to be serious enough to compromise the reliability of the certainty of conclusions.

Implementation of the ACT watchful waiting (research question 1)

The G-BA specified watchful waiting as the ACT for research question 1.

CLARITY AD used placebo as comparator therapy. The study was not designed for a comparison with watchful waiting. However, the study is suitable for such a comparison. This is explained below.

The following examinations were carried out in the CLARITY AD study to assess symptoms and health status:

- Regular MRI scans throughout the course of treatment
- Regular visits to record symptoms and health status (every 3 to 6 months)

As already described, the current S3 guideline also recommends non-drug therapies such as cognitive training, cognitive stimulation or physical exercise for both of these patient groups [5]. Non-drug therapies were permitted during the study; however, no data are available on the proportion and type of non-drug therapies used during the study (see also the previous section).

The study provided for regular MRI scans to be carried out throughout the course of treatment. Currently, this is not recommended in the guidelines in the context of treatment with anti-dementia therapies (relating to research question 2) or in the absence of treatment [5]. The study involved regular visits (every 3 to 6 months). Furthermore, the S3 guideline does not specify any further recommendations for action or specific parameters to be monitored.

Despite the uncertainties described, the measures taken in the placebo arm are generally regarded as a sufficient approximation to the ACT watchful waiting in this clinical setting.

I 4 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 (see Table 4).

I 4.1 Study characteristics (specific to research question 1)

For characteristics of the studies that apply to all research questions, see Section I 3.2.

I 4.1.1 Patient characteristics

Table 9 shows the characteristics of the patients in the subpopulation of the included study relevant for research question 1.

Table 9: 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] = 252	Placebo N[a] = 245
CLARITY AD		
Age [years], mean (SD)	ND	ND
Sex [F/M], %	ND	ND
Region (IxRS), n (%)	ND	ND
ApoE ε4 carrier status by genotype (laboratory), n (%)		
Heterozygotes	ND	ND
Non-carriers	ND	ND
CDR-GS		
0.5 (very mild dementia)	ND[b]	ND[b]
1 (mild dementia)	ND[b]	ND[b]
CDR-SB	N[c] = 242	N[c] = 240
Mean (SD)	2.6 (1.07)	2.7 (1.09)
Median [Q1; Q3]	ND	ND
MMST	ND	ND
ADAS-Cog14	N[c] = 242	N[c] = 240
Mean (SD)	22.1 (6.66)	21.4 (6.94)
Median [Q1; Q3]	ND	ND
EQ-5D VAS	N[c] = 242	N[c] = 240
Mean (SD)	82.2 (13.09)	81.2 (13.08)
Median [Q1; Q3]	ND	ND

Table 9: 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] = 252**	**Placebo N[a] = 245**
QOL-AD	N[c] = 242	N[c] = 240
Mean (SD)	39.3 (6.13)	39.4 (6.07)
Median [Q1; Q3]	ND	ND
Age at initial onset of symptoms [years], n (%)	ND	ND
Age group at initial onset of symptoms [years], n (%)	ND	ND
Time since initial onset of symptoms [years], mean (SD)	ND	ND
Age at diagnosis [years], n (%)	ND	ND
Age group at diagnosis [years], n (%)	ND	ND
Time since diagnosis [years], n (%)	ND	ND
Treatment discontinuation, n (%)	ND	ND
Study discontinuation, n (%)	ND	ND

a. Number of randomized patients who received at least one dose of the respective treatment. Values that are based on other patient numbers are marked in the corresponding column if the deviation is relevant.
b. According to the inclusion criteria, patients with MCI must have a CDR-GS of no more than 0.5.
c. Number of randomized 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 data correspond to the baseline values of the respective instruments.

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 company does not provide any information on the characteristics of the population. It is possible to derive individual data on values at the time of randomization from the results for outcomes that are analysed on a continuous basis. The characteristics of patients with MCI without anti-dementia drugs (subpopulation without consideration of the approval requirements) are set out as supplementary information in the Appendix (see Table 21 in I Appendix C.1 of the full dossier assessment). Taking these details into account, the patients in the relevant subpopulation are described in more detail below.

The mean age of the patients was around 70 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 a few years before they reached the age of 70.

At the start of the study, patients in the relevant subpopulation had a CDR-SB of 2.6 and 2.7 respectively. Given a scale range of 0 to 18, this score corresponds to the stage of very mild

dementia (see also I Appendix E.2 of the full dossier assessment) [42]. At baseline, the scores on the Alzheimer's Disease Assessment Scale – Cognitive subscale (14-item version) (ADAS-Cog14) stood at 22 and 21 respectively, on a scale ranging from 0 to 90, with higher scores indicating more severe cognitive impairment [43]. The scores on the Quality of Life in Alzheimer's disease (QOL-AD) instrument, used to assess quality of life in people with Alzheimer's disease, averaged 39 on a scale ranging from 13 to 52, with higher scores indicating a better quality of life [44]. Further details on the instruments mentioned can be found in Section I 4.2.1. No data on the CDR-GS or the MMST at baseline were available for the populations described, even though these had been defined as inclusion criteria for the study.

Moreover, there are no data on treatment discontinuation for the relevant subpopulation. In the MCI population without anti-dementia drugs (without consideration of the regulatory requirements), more patients in the intervention arm discontinued treatment prematurely than in the control arm (17% vs. 14%; Table 21 in I Appendix C.1 of the full dossier assessment). Common reasons for treatment discontinuation were AEs, withdrawal of consent and patient decision. No data are available on study discontinuation. The data in the study report show that, in the total population, the majority of patients who discontinued treatment (22% vs. 17%) also discontinued the study (19% vs. 16%).

Overall, the demographic and clinical characteristics of the patients included are considered to be sufficiently comparable. A comparison of the characteristics of the MCI population with those of the population with mild Alzheimer's dementia can be found in Section I 5.1.1.

Concomitant treatments

In accordance with the study's inclusion criteria, the concomitant anti-dementia treatment had to have been maintained at a stable dose for at least 12 weeks prior to baseline (see also Section I 3.2.1). It is unclear to what extent, as part of the study inclusion (e.g. 12 weeks before baseline) changes to the therapy (discontinuation or initiation) were still being made with a view to treatment optimization or review of the diagnosis. Information on the duration of prior treatment was requested but is not available. Research question 1 only considered patients with MCI without anti-dementia treatment for Alzheimer's disease. The initiation of concomitant anti-dementia drug therapy should be avoided, but was possible where medically necessary.

No data are available on concomitant therapies at baseline or during the course of the study for the relevant subpopulation. Data on the population of patients with MCI and without anti-dementia drugs at the start of the study (not taking into account regulatory requirements) are set out in I Appendix C.1 of the full dossier assessment, Table 22.

In patients with MCI without anti-dementia drugs at baseline, concomitant therapy was initiated during the course of the study in approximately 10% of patients in both study arms, mostly with donepezil. A small proportion of patients began treatment with memantine, which is only approved from the stage of moderate dementia onwards (see also the section 'Administration of memantine and anticoagulants during the course of the study' in Section I 3.2.3.3).

I 4.1.2 Risk of bias across outcomes (study level)

Table 10 shows the risk of bias across outcomes (risk of bias at study level).

Table 10: Risk of bias across outcomes (study level) – RCT, direct comparison: lecanemab vs. placebo

Study	Adequate random sequence generation	Allocation concealment	Blinding		Reporting independent of the results	No additional aspects	Risk of bias at study level
			Patients	Treating staff			
CLARITY AD	Yes	Yes	Yes	Yes	Yes	Yes	Low
RCT: randomized controlled trial							

The risk of bias across outcomes was rated as low for the study.

I 4.1.3 Transferability of the study results to the German health care context

The company stated that the results of the CLARITY AD study were transferable to the German health care context due to the study design, the study population and the intervention. It further states that the vast majority of patients included had Caucasian family origin, that the study centres were mainly located in North America, Europe and Australia, and that the vast majority of the study population would therefore have been treated to high standards comparable to those in Europe. It explains that, with the exception of the inclusion of patients with homozygous ApoE ε4 carrier status and the use of anticoagulants, the inclusion criteria for the study population correspond to the patient group with early-stage Alzheimer's disease who, in everyday German clinical practice, would be eligible for treatment with lecanemab in accordance with the SmPC. From the company's perspective, the proportion of patients with homozygous ApoE ε4 carrier status and the average age of the study participants are comparable to the German health care context. In the study, lecanemab was applied and dosed in accordance with the specifications of the SmPC.

Furthermore, the company describes the use of AChEIs in patients with mild Alzheimer’s dementia as being indicated and appropriate within the German health care context. According to the company, patients with MCI – particularly those with proven positive biomarkers – are often prescribed AChEIs off-label in clinical practice. It goes on to explain that, in clinical practice, there is also a significant proportion of patients with mild Alzheimer’s dementia for whom treatment with AChEIs is not indicated. The company states that, in clinical practice, patients with early-stage Alzheimer’s dementia are also treated with memantine on an off-label basis, at the discretion of the treating physician.

Overall, the patients in the CLARITY AD study were treated in line with the German health care context and routine care, and the results are therefore transferable to the German health care context.

The company did not provide any further information on the transferability of the study results to the German health care context. For the transferability of the study results, see also Sections I 3.2.2.1 and I 3.2.3.

I 4.2 Results on added benefit

I 4.2.1 Outcomes included

The following patient-relevant outcomes were to be included in the assessment:

- Mortality
  - all-cause mortality
- Morbidity
  - symptoms recorded using the CDR-SB
  - cognition recorded using the ADAS-Cog14
  - independence in everyday life
  - behavioural changes
  - health status recorded using the EQ-5D VAS
- Health-related quality of life
  - recorded with the Quality of Life - Alzheimer's Disease (QOL-AD) instrument
- Side effects
  - SAEs
  - discontinuation due to AEs
  - symptomatic ARIA events

- infusion related reaction (AEs)
- other specific AEs, if any

The selection of patient-relevant outcomes deviated from that of the company, which used further outcomes in the dossier (Module 4 A).

Table 11 shows for which outcomes data were available in the included study.

Table 11: Matrix of outcomes – RCT, direct comparison: lecanemab versus placebo

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 reaction[c] (AEs)	Other specific AEs
CLARITY AD	Yes	Yes	Yes	No[d]	No[d]	Yes	Yes	Yes	Yes	No[d]	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 using a PT list compiled by the company; for further details, see the text below.
d. No suitable data available; see text below for explanation.
e. No suitable analyses on AEs available, a choice of further specific AEs is therefore impossible.

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; PT: Preferred Term; QOL-AD: Quality of Life in Alzheimer's Disease Scale; RCT: randomized controlled trial; SA: serious adverse event; VAS: visual analogue scale

Analyses at Month 18 were used for the benefit assessment

The company mainly presented analyses on Month 18 in its dossier. Given the 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 relating to morbidity and quality of life. There was no information on observation periods for the relevant subpopulations. However, based on the available data (see I Appendix C of the full dossier assessment, Table 23 and Table 26), it can be assumed that the duration of follow-up in both study arms was sufficiently comparable. The analyses of the relative risk (RR) at Month 18 are therefore used in the current data situation.

Outcomes on morbidity

Symptoms (CDR-SB)

The CDR is a widely used tool for recording the severity of symptoms in patients with Alzheimer's disease. The study is conducted in the form of semi-structured interviews with both a carer (usually the patient's partner) and the patient. It is a complex scale comprising a total of six domains: three cognitive domains (memory, orientation, judgement and problem-solving) and three functional domains (community life, housekeeping and hobbies, and personal hygiene). The patient is only interviewed in relation to the three cognitive domains, whilst the carer is the sole person asked about the three functional domains. For each of the six domains, the interviewer subjectively assesses the respective degree of impairment on a 5-point ordinal scale, to which numerical values from 0 to 3 are assigned (0 = none, 0.5 = questionable, 1 = mild, 2 = moderate, 3 = severe) [45,46].

Based on the six domain scores, two different overall scores can be calculated: CDR-GS and CDR-SB.

The CDR-GS distinguishes between five stages of disease severity, each of which is assigned a point value corresponding to the gradations in the domain scores: no dementia (0 points), questionable dementia (0.5 points), mild dementia (1 point), moderate dementia (2 points) or severe dementia (3 points) [45,46]. As there is no direct correlation between the respective score value and the actual severity of the disease at each stage, this is an ordinal scale. The CDR-GS is calculated using an algorithm in which, amongst other things, the 'memory' domain is given greater weight than the other five domains. Consequently, it is possible for changes in the course of the disease to occur across several domains, which, however, are not reflected in the total CDR-GS score [42,47].

The CDR-SB is calculated by adding the six domain scores together to produce a summary score, so that the CDR-SB has a scale range of 0 to 18, with a higher score indicating more pronounced symptoms and functional restrictions. Each of the six domains contributes equally to the CDR-SB, and any change in one of the six domains has an immediate effect on the CDR-SB [42,48,49]. Compared with the CDR-GS, the CDR-SB exhibits greater sensitivity, particularly in early-stage Alzheimer's disease, and is better able to distinguish between MCI and mild dementia. For example, a patient with a CDR-GS score of 0.5 may have CDR-SB scores ranging from 0.5 to 5 [42,47,49,50].

CDR analyses in the form of CDR-SB are preferred over those using the CDR-GS for the assessment of symptoms, particularly in early-stage Alzheimer's disease, due to the CDR-SB's greater sensitivity, and are used for the benefit assessment.

The company submits analyses for the CDR-SB on deterioration by the post hoc threshold of 2.7 points. Unlike the CDR-GS, the CDR-SB can be assumed to use interval scaling [47] meaning

that responder analyses on changes by a proportion of the scale range can be interpreted. The threshold value of 2.7 points corresponds exactly to 15% of the scale range. As explained in the IQWiG *General Methods* [1], for a response criterion to reflect with sufficient certainty a patient-noticeable change, it should correspond to at least 15% of the scale range of an instrument if prespecified and exactly 15% of the scale range in post-hoc analyses. In the CDR-SB, changes can only be represented in increments of 0.5 or as whole numbers (see I Appendix E.2 of the full dossier assessment). A patient's condition may therefore deteriorate by 2.5 or 3 points, but not by 2.7 points. It is therefore assumed that the company classified patients as responders once their condition had deteriorated by at least 3 points. The responder analyses for the CDR-SB submitted by company concurred with the requirements of the methods paper and were used for the benefit assessment.

In addition, the company provides prespecified analyses of changes at Month 18 based on the mixed-effects model with repeated measures. These are presented as supplementary information in I Appendix E.1 of the full dossier assessment. For several populations, the company also provides mean values for the scores in the individual domains at all observation time points, including the number of patients included in the respective analyses. It does not provide this information for the relevant subpopulations. However, these would be helpful in order to fully interpret the changes in the CDR-SB total score. It would be even more informative to provide information on how many patients were in which category (0, 0.5, 1, 2, 3) in the respective domains at baseline and over the course of the study. In order to contextualise the changes in the CDR-SB, additional charts and analyses for the CDR-SB and its associated domains are presented as supplementary information in I Appendix E of the full dossier assessment for both the total population and certain subpopulations.

Furthermore, in Module 4A, the company presents analyses for the CDR-GS in the form of time-to-event analyses on confirmed deterioration by a post hoc response criterion classified according to disease stage at baseline (time to confirmed deterioration by 0.5 points for MCI at baseline, or by 1 point for mild Alzheimer's dementia at baseline). Confirmed deterioration was defined as a deterioration by the response criterion at two consecutive visits. Missing values were not imputed. According to the study design, time-time-to-event analyses on confirmed deterioration by a deviating response criterion (time to confirmed deterioration by 0.5 points, regardless of disease stage at baseline) were predefined for the CDR-GS. In Module 4 A, the company did not present any analyses relating to this prespecified response criterion. As interval scaling cannot be assumed for the CDR-GS, analyses based on continuous data (i.e. both MMRM and responder analyses on deteriorations by a specific score value) are not appropriate. At best, the CDR-GS categories could be used to assess disease progression. To this end, it would be necessary to identify a permanent deterioration to a CDR-GS score of at least 1 in patients with MCI and a maximum CDR-GS score of 0.5. For patients with mild Alzheimer's dementia and a maximum CDR-GS of 1, the permanent deterioration to a CDR-GS

of at least 2 would need to be recorded. However, it is questionable whether the CDR-GS could be used to assess disease progression, as the diagnosis of MCI versus mild Alzheimer's dementia, in particular, is more complex and currently cannot be captured by a single instrument. In this context, it would seem more sensible to review the physicians' diagnosis during the course of the study and thus assess the progression to a later stage of the disease.

Regardless of this, time-to-event analyses for the CDR-SB covering the time to deterioration of at least 3 points would be desirable for the assessment of symptoms. However, unlike in the EPAR (where the thresholds are ≥ 0.5 points and ≥ 2 points), the dossier does not provide any time-to-event analyses [51].

Cognition (ADAS-Cog14)

The ADAS-Cog is a functional test that was originally developed to assess the severity of cognitive impairment in Alzheimer's dementia and is widely used in this therapeutic indication. In its original version, it comprises 11 items (ADAS-Cog11) [52,53]. Subsequent studies have identified further items which are intended, amongst other things, to improve sensitivity to changes in the early stages of the disease [53,54]. In addition to the original 11 items, the ADAS-Cog14 also includes three of these additional items: delayed Word Recall (recalling words after a delay), Number Cancellation (crossing out specific digits from a series of numbers) and Maze Task/Executive Function (finding one's way through a maze image). The survey takes the form of an interview with the patient. The items include both tasks to be carried out by the patient themselves (for example, relating to temporal and spatial orientation) and subjective assessments made by the interviewer (for example, regarding speech comprehension). Each of the 14 items in the ADAS-Cog14 is rated on a scale of 0 to 5 or 0 to 10 [55]. The scores for all items are added together to give a sum score, so that the ADAS-Cog14 scale ranges from 0 to 90, with a higher score indicating more severe cognitive impairment.

The company submits analyses on deterioration by the post hoc threshold of 13.5 points for the ADAS-Cog14, which corresponds to exactly 15% of the scale. As explained in the IQWiG *General Methods* [1], for a response criterion to reflect with sufficient certainty a patient-noticeable change, it should correspond to at least 15% of the scale range of an instrument if prespecified and exactly 15% of the scale range in post-hoc analyses. The responder analyses for the ADAS-Cog14 submitted by company therefore concurred with the requirements of the methods paper and were used for the benefit assessment.

Independence in everyday life

Significance in the therapeutic indication

As dementia progresses, cognitive functions and everyday skills deteriorate and are lost; as the disease advances, this leads, amongst other things, to a loss of independence and

autonomy [5,56]. The severe stage of dementia is often characterized by complete dependence on one's surroundings. This affects not only complex everyday functioning, but increasingly also basic competencies such as personal hygiene, food preparation, mobility and judgement. This is just as stressful for those affected as it is for their families.

As a rule, the outcome independence in everyday life is therefore relevant to patients [33,56,57]. One operationalization to be discussed would be, for example, the need for complete inpatient care or institutionalized outpatient care. Another possible approach would be an operationalization as the time of transition to moderate Alzheimer's dementia, which is associated with significant limitations in independence. Functional abilities could also be identified using suitable instruments that take into account the concepts of basic self-care tasks and/or instrumental activities of everyday life [5,57,58]. However, it must be assumed that an 18-month follow-up period is insufficient to obtain informative results regarding these longer-term outcomes in patients with MCI due to Alzheimer's disease or mild Alzheimer's dementia at baseline, (see also Section I 3.2.3.1).

Activities of daily living (ADCS-MCI-ADL)

The Alzheimer's Disease Cooperative Study Mild Cognitive Impairment Activities of Daily Living Inventory (ADCS-MCI-ADL) is a tool for recording impairment in activities of daily living in patients with MCI through third-party assessment [43,59]. It was derived from the original ADCS-ADL [60], which was developed to record impairment in activities of daily living (ADL) in patients with Alzheimer's dementia. The ADCS-MCI-ADL is available in an 18-item version (ADCS-MCI-ADL18), which was also used in the company's CLARITY AD study, and in a 24-item version (ADCS-MCI-ADL24), which includes six additional questions relating specifically to patients with MCI [43]. The recording takes the form of an interview with a person who usually lives with the patient or spends time with them on a regular basis (for example, the patient's partner); there is no patient-reported recording of activities of daily living [43,60].

The outcome Activities of Daily Living, as a possible operationalization of independence in everyday life, is relevant to patients. However, the ADCS-MCI-ADL is not considered a validated instrument for recording activities of daily living in patients with MCI or mild dementia due to Alzheimer's disease and is therefore not used for this benefit assessment. This was due to a lack of information on the content validity, in particular on the involvement of patients in the therapeutic indication for the development of the instrument. Furthermore, the ADCS-MCI-ADL is exclusively recorded through third-party assessment, although it can be assumed that patients with MCI or mild dementia are, for the most part, still able to assess for themselves any impairment in their activities of daily living. Furthermore, the sources provided do not show that the ADCS-MCI-ADL is designed for patients with mild dementia caused by Alzheimer's disease, in addition to patients with MCI.

Behavioural changes

As the disease progresses, mental and behavioural symptoms develop in the vast majority of the patients [5]. These include, for example, depression, anxiety and apathy, but also aggression, psychotic symptoms, disinhibited behaviour or sleep disorders. On the one hand, these are a consequence of the disease, which leads to impairments in temporal and spatial orientation, communication skills, autobiographical identity and personality traits. On the other hand, they may be a reflection of the high levels of emotional distress caused by the diagnosis, the increasing impairment and the resulting social isolation [5,57]. Therefore, the outcome behavioural changes is, in principle, relevant to patients [56,57].

In the study, suicidal tendencies were recorded at various points in time using the Columbia Suicide Severity Rating Scale (C-SSRS). However, it is unclear how suicidal tendencies were operationalized. Furthermore, results for the relevant subpopulations are not available. Irrespective of this, whilst suicidal tendencies are one component of potential psychopathological symptoms, as a sole outcome they do not fully reflect relevant behavioural changes in the present therapeutic indication.

Alzheimer's Disease Composite Score (ADCOMS)

The ADCOMS was designed to record clinical deterioration in patients with prodromal Alzheimer's disease or mild Alzheimer's dementia. This is not a standalone instrument, but rather a composite scale comprising items/domains from the following instruments [61]:

- ADAS-Cog12: 4 items (Delayed Word Recall, Orientation, Word Recognition, Word Finding Difficulty)
- MMST: 2 items (Orientation Time, Drawing)
- CDR-SB: all 6 domains (Memory, Orientation, Judgement and Problem Solving, Community Affairs, Home and Hobbies, Personal Care)

The result of the CDR-SB is therefore incorporated in full into the ADCOMS, with a weighting of approximately 70% [62]. Similarly, the four items from the ADAS-Cog12 included in the ADCOMS are also included in the ADAS-Cog14. The ADCOMS is therefore redundant in relation to the CDR-SB and the ADAS-Cog14 and is consequently not used for the benefit assessment. Regardless of this, the results of the responder analyses for the ADCOMS presented in Module 4A, showed no statistically significant differences between the study arms in the subpopulations relevant to the assessment.

Biomarker-associated outcomes not relevant to patients

In the dossier, the company presents several biomarker-associated outcomes relating to amyloid and tau pathology in order to demonstrate the effectiveness of lecanemab with regard to the pathomechanisms underlying Alzheimer's disease. The diagnosis was made

using imaging techniques and cerebrospinal fluid analysis. Relevant for a benefit assessment are patient-noticeable symptoms associated with the change in amyloid and Tau pathologies or the associated reduction in health-related quality of life. The company did not present a surrogate validation using a biomarker-associated outcome as a surrogate for a patient-relevant outcome. The biomarker-associated outcomes were therefore not used for this benefit assessment.

Health-related quality of life (QOL AD)

The QOL-AD is an instrument for the recording of health-related quality of life in patients with Alzheimer's disease. The instrument comprises a total of 13 items and records health-related quality of life separately through self-assessment and third-party assessment. The patient's self-assessment takes the form of a structured interview based on a questionnaire covering the 13 items, with instructions for the interviewer. The third-party assessment is carried out by a family member or another carer using a questionnaire comprising the same 13 items. Each of the 13 items in the QOL-AD is rated on a scale of 1 to 4 (1 = poor, 2 = fair, 3 = good, 4 = excellent). The scores for all 13 items are added together to produce a sum score, so that the scale ranges from 13 to 52, with a higher score indicating a better health-related quality of life [44,63].

The validation study on the development of the QOL-AD did not distinguish between MCI and dementia. The study included individuals with MCI due to Alzheimer's disease (mean MMST score 22, range 18 to 28) [63]. It is therefore assumed that the QOL-AD is, in principle, suitable for assessing the quality of life of people with early-stage MCI as well as those with early-stage mild dementia.

The validation study also shows that individuals with an MMST score of ≥ 10 are usually able to complete the QOL-AD themselves [63]. In the CLARITY AD study presented by the company, patients in both study arms had a median MMST score of 25 (range 22 to 30) at baseline. It is therefore assumed that the majority of patients in the CLARITY AD study were able to complete the QOL-AD themselves; consequently, the patient-reported version of the QOL-AD is used for this benefit assessment. In the CLARITY AD study, the QOL-AD was recorded both in the patient-reported version and the third-party-reported version. Based on the information provided in Module 4A, it is assumed that the QOL-AD analyses presented there only include patient-reported outcomes.

The company submits analyses on deterioration by the post hoc threshold of 5.85 points for the QOL-AD, which corresponds to exactly 15% of the scale. As explained in the IQWiG *General Methods* [1], for a response criterion to reflect with sufficient certainty a patient-noticeable change, it should correspond to at least 15% of the scale range of an instrument if prespecified and exactly 15% of the scale range in post-hoc analyses. The responder analyses for the QOL-

AD submitted by the company therefore concurred with the requirements of the methods paper and were used for the benefit assessment.

Side effects

Recording of AEs and SAEs in the study

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. The company presented the analyses in the dossier. The company further states that, for patients who discontinued treatment – but not the study at the same time – it was intended that, following the follow-up visit, they would attend every scheduled visit at which clinical assessments on outcomes of the morbidity and side effects categories were carried out in accordance with the study design. Accordingly, some of the patients continued to be monitored even after treatment had been discontinued. However, data on treatment or study discontinuations or regarding observation periods are not available for the relevant subpopulations, and relevant conclusions based on other populations are only possible to a limited extent.

Given the current data situation, the available analyses on AEs can be considered in part (see the following sections), although it would be desirable to have analyses extending beyond treatment discontinuation.

Recording of disease-related events

The company presented analyses with and without disease-related events for the outcomes AEs and SAEs. It considers the following preferred terms (PTs) according to the Medical Dictionary for Regulatory Activities (MedDRA) to be disease-related events: Alzheimer's-type dementia, Alzheimer's-type dementia without complications, Alzheimer's-type dementia with delirium, Alzheimer's-type dementia with delusions, Alzheimer's-type dementia with depressive mood, prodromal Alzheimer's disease, familial Alzheimer's disease with early initial manifestation. This appears to be appropriate for this therapeutic indication. Therefore, the overall SAE rate without disease-related events is used for this benefit assessment.

Incomplete data on common AEs

According to the dossier template, in addition to the overall AE rates, results on all AEs (operationalized as MedDRA System Organ Class (SOC) and Preferred Terms [PTs]) are to be presented if they exceed a certain minimum frequency [64]. Module 4A, Appendix 4-G presents the AEs for the subgroup 'non-carriers or heterozygotes not taking anticoagulants at baseline' for the populations with MCI not taking anti-dementia drugs and mild Alzheimer's dementia receiving AChEI therapy (subpopulation without consideration of the regulatory requirements). However, the information on AEs at SOC and PT level presented by the company in Module 4A, Appendix 4-G was not complete. Results are available only with regard to SOC and PT, for which statistically significant differences between the arms were observed

in the subpopulations MCI without anti-dementia drugs and mild Alzheimer's dementia with AChEI therapy (subpopulation without consideration of the regulatory requirements). Consequently, it is unclear whether other SOCs and PTs also met the criterion of ≥ 10 patients in at least one study arm that were not presented in Appendix 4-G. The common SOCs and PTs for research question 1 and research question 2 presented in I Appendix H of the full dossier assessment are therefore potentially incomplete.

Symptomatic ARIA events

ARIA summarizes the radiologically detectable changes in cerebral imaging that occur in patients with Alzheimer's disease under treatment with amyloid-lowering therapies [39,41]. ARIA typically occurs at an early stage of treatment and is usually asymptomatic [39]. Nevertheless, ARIA may be associated with typical symptoms such as headaches, confusion, vision disorders, nausea and gait disorders, and in rare cases may present as serious and life-threatening events, including seizures and status epilepticus [39-41]. ARIA, as well as any associated symptoms, usually subside within weeks to months of treatment discontinuation [40,41]. If treatment is continued, ARIA may recur [41].

ARIA are categorized as ARIA-E and ARIA-H [39-41]. In doing so, ARIA-E are characterized by parenchymal oedema, whilst ARIA-H are characterized by cerebral micro- and/or macrobleeds, superficial siderosis and sulcal or leptomeningeal haemosiderin deposits [39-41]. ARIA-E and ARIA-H may occur independently of each other or together. 50% of patients also develop ARIA-H before or after the occurrence of ARIA-E [40]. Classification can be based on radiological severity [40,41]. In cases of mild, asymptomatic ARIA, treatment may be continued [25,40]. In cases of symptomatic and radiologically moderate to severe ARIA-E, or symptomatic and radiologically moderate ARIA-H, treatment is to be interrupted and the decision to resume treatment once the symptoms have subsided should be carefully considered. According to the SmPC, treatment must be permanently discontinued if radiologically severe ARIA-H and symptomatically severe ARIA-E and ARIA-H occur.

Asymptomatic ARIA are not directly perceivable by the patient and are therefore not patient-relevant per se. However, the occurrence of radiologically moderate to severe ARIA has therapeutic implications. In contrast, symptomatic ARIA-E and ARIA-H are directly relevant to patients because of the associated symptoms. Likewise, serious ARIA-E and ARIA-H are classified as relevant to patients. In the dossier, the company presents analyses of serious ARIA-E and ARIA-H for various sub-populations. However, results for the relevant subpopulations are not available. The study report and the primary publication [31] present prespecified analyses of symptomatic ARIA-E and ARIA-H for the total population. However, in its dossier, the company did not present corresponding analyses for the relevant subpopulations.

In summary, symptomatic ARIA events are classified as relevant to the patient and are taken into account for this benefit assessment. The following events are considered: symptomatic ARIA-E and ARIA-H, as well as serious ARIA-E and ARIA-H. However, results for the relevant subpopulations are not available. The missing analyses must be submitted during the commenting procedure. In addition, combined analyses of the events under consideration are also required. I Appendix G of the full dossier assessment also presents the results for other populations as supplementary information.

Infusion related reaction (AEs)

In the CLARITY AD study, infusion-related reactions were recorded as 'study-specific AEs' using a prespecified PT list. According to the information in the study protocol, events that had occurred during the infusion or up to 24 hours after the end of the infusion were documented as infusion-related reactions. The following events (PTs) were recorded: 'infusion-related reactions' and 'injection site reactions'. However, other events which may also be related to an infusion, such as anaphylactic reactions, drug hypersensitivity, hypersensitivity or cytokine release syndrome, were not recorded within this outcome. Furthermore, this list does not include the symptoms underlying infusion-related reactions (e.g. chills, headaches, nausea or fever), but rather the diagnosis (e.g. infusion-related reaction). On the basis of the available information, it can therefore be assumed that, when assessing whether a symptom (e.g. fever) was classified as an infusion-related reaction, no specific criteria were specified. Only in certain data constellations, e.g. in the presence of marked effects (see dossier assessment A21-60 [65]), it is conceivable to derive greater or lesser harm based on such an operationalization. This is the kind of data constellation we are dealing with here.

Furthermore, the company does not comment in the dossier on whether the events underlying the outcome infusion-related reaction (e.g. headaches) were also included in the analyses of AEs. In case that the PT events were not recorded in the general AE analysis, the interpretability of the common PTs/SOCs might be limited (see A21-60 [65]). In this case, the events under the symptoms concerned (e.g. the PT headache) would not be fully recorded in the analyses on PT/SOC presented by the company in Module 4A.

In summary, the operationalization is regarded as a suitable means of mapping infusion-related reactions and is used in the present data constellation for the benefit assessment. The analyses at AE level presented by the company were used for the outcome infusion-related reactions irrespective of the severity.

I 4.2.2 Risk of bias

Table 12 describes the risk of bias for the results of the relevant outcomes.

Table 12: Risk of bias across outcomes and outcome-specific risk of bias – RCT, direct comparison: lecanemab versus placebo

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 reaction[c] (AEs)	Other specific AEs
CLARITY AD	L	H[d]	H[e]	H[e]	–[f]	–[f]	H[e]	H[e]	H[d]	L[g]	–[f]	H[d]	–[h]

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 using a PT list compiled by the company; for details, see Section I 4.2.1.
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 reasoning, see Section I 4.2.1 of this dossier assessment.
g. Despite the low risk of bias, the certainty of results is presumably limited for the outcome of discontinuation due to AEs.
h. No suitable analyses on AEs available, a choice of further specific AEs is therefore impossible.

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; SA: serious adverse event; VAS: visual analogue scale

The risk of bias was rated as high for the results for all outcomes except the outcome discontinuation due to AEs.

For the outcomes on morbidity and health-related quality of life, for which suitable data are available, the high risk of bias stems from a high proportion of patients not included in the analysis (> 10%) or from large differences between the treatment groups (> 5 percentage points). Only patients for whom values at both baseline and Month 18 were available were included in the analysis. Data on missing values in the relevant subpopulations in the course of the study are lacking.

For the outcomes SAEs and infusion-related reactions, the outcome-specific risk of bias was rated as high. This is due to incomplete observations for potentially informative reasons, as AEs were only included in the analyses for up to 30 days after treatment discontinuation.

The risk of bias for the outcome discontinuation due to AEs is rated as low. However, the certainty of results was limited by the fact that treatment might also be discontinued for reasons other than AEs. These reasons represented a competing event for the outcome to be recorded, discontinuation due to AEs. This means that, although AEs that would have led to discontinuation of therapy may occur after discontinuation for other reasons, the criterion discontinuation is no longer applicable to them. It was impossible to estimate how many AEs this affected. Detailed information on treatment and study discontinuations as well as on reasons for discontinuation is not available for the relevant subpopulation.

Since no suitable analyses are available for the outcomes independence in everyday life, behavioural changes and symptomatic ARIA events (see Section I 4.2.1), the risk of bias for these outcomes was not assessed.

Consideration of further aspects on the certainty of conclusions

The following aspects must be taken into account in the assessment of the certainty of conclusions:

- Lack of data on the use of AChEIs (only in cases of mild Alzheimer's dementia)
- Lack of specifications on how to deal with a lack of efficacy or progression to the next stage
- Lack of information on non-drug therapies

Detailed explanations are described in Section I 3.2.3. The certainty of conclusions of the study results for the given research questions was therefore reduced.

Summary assessment of the certainty of conclusions

Based on the available information from the CLARITY AD study, at most hints, e.g. of an added benefit, could be derived for all outcomes presented.

I 4.2.3 Results

Table 13 summarizes the results 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. Where necessary, calculations conducted by the Institute are provided in addition to the data from the company's dossier.

Tables on common AEs, common SAEs and discontinuations due to AEs are presented in I Appendix H.1 of the full dossier assessment.

Table 13: Results (mortality, morbidity, health-related quality of life, side effects) – 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]		ND[b]		ND[b]	ND[c]
Morbidity					
Symptoms (CDR-SB – deterioration at Month 18[d])	216	22 (10.2)	217	25 (11.5)	0.88 [0.52; 1.52]; 0.655[e]
Cognition (ADAS-Cog14 – deterioration at Month 18[f])	213	11 (5.2)	215	12 (5.6)	0.93 [0.42; 2.05]; 0.848[e]
Independence in everyday life				No suitable data[g]	
Behavioural changes				No suitable data[g]	
Health status (EQ-5D VAS – improvement at Week 18[h])	216	37 (17.1)	218	36 (16.5)	1.04 [0.68; 1.58]; 0.864[e]
Health-related quality of life					
QOL-AD – deterioration at month 18[i])	216	21 (9.7)	217	21 (9.7)	1.00 [0.57; 1.79]; 0.987[e]
Side effects					
AEs (supplementary information)[j]	252	226 (89.7)	245	208 (84.9)[k]	–
SAEs[j]	252	37 (14.7)	245	28 (11.4)	1.28 [0.81; 2.03]; 0.293[l]
Discontinuation due to AEs	252	11 (4.4)	245	7 (2.9)	1.53 [0.60; 3.88][e]; 0.530[f]
Symptomatic ARIA events		ND[m]		ND[m]	ND[m]
Infusion related reaction (AEs)[n]	252	67 (26.6)	245	19 (7.8)	3.43 [2.13; 5.53]; < 0.001[l]
Other specific AEs				No suitable data[o]	

Table 13: Results (mortality, morbidity, health-related quality of life, side effects) – 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
a. The results on all-cause mortality are based on the information on fatal AEs. b. Data for the relevant subpopulation are not available; in the subpopulation of patients with MCI without anti-dementia drugs (without consideration of the regulatory requirements) at baseline, there were 3 deaths in the lecanemab arm and no deaths in the placebo arm. c. Based on the available data on the MCI population without anti-dementia drugs (without consideration of the regulatory requirements), it can be estimated with sufficient certainty that no statistically significant result is to be expected in the relevant subpopulation either. 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). Further interpretation of the data is impossible due to the lack of information on the domains and distributions for the relevant subpopulations. e. Unstratified logistic regression model. f. 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). g. See Section I 4.2.1 of the present dossier assessment for the reasoning. h. 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). i. 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). j. Excluding disease-related events (see Section I 4.2.1). k. Discrepancy between Module 4A and Module 5 of the dossier. The presented figures were taken from additional analyses in Module 5 [26]. l. Institute's calculation, unconditional exact test (CSZ method according to [66]). m. No data are available for the relevant subpopulation; results for other populations are presented as supplementary information in I Appendix G of the full dossier assessment. n. Operationalized via a PT list compiled by the company. o. No suitable analyses on AEs available, a choice of further specific AEs is therefore impossible. 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; n: number of patients with (at least one) event; N: number of analysed patients; ND: no data; 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					

Based on the available information, at most hints, e.g. of an added benefit, could be determined for all outcomes (see Section I 4.2.2).

Mortality

All-cause mortality

There are no data on deaths during the course of the study for the relevant subpopulation. Based on the available data on the MCI population without anti-dementia drugs (without consideration of the regulatory requirements), it can be estimated with sufficient certainty that no statistically significant result is to be expected in the relevant subpopulation either.

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 the treatment groups (see Table 28 and Figure 5 in Appendix E.1 of the full dossier assessment).

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.

Independence in everyday life

No suitable data were available for the outcome independence in everyday life (see Section I 4.2.1 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 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.

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.

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

There are no data on symptomatic ARIA events during the course of the study for the relevant subpopulation. There was no hint of greater or lesser harm from lecanemab in comparison with watchful waiting; an added benefit is therefore not proven. However, based on the results from other populations, a greater harm from lecanemab compared with watchful waiting cannot be ruled out (see Table 29 in I Appendix G of the full dossier assessment).

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.

Other specific AEs

No suitable data were available for further specific AEs (see Section I 4.2.1 for reasoning). There was no hint of greater or lesser harm from lecanemab in comparison with watchful waiting; greater or lesser harm is therefore not proven.

Results for the pooled subpopulation for research question 1 and research question 2

The pooled results for the populations relating to research questions 1 and 2 are also presented in I Appendix D of the full dossier assessment. The results of this largest possible population under consideration of the requirements of the marketing authorization and the ACT are comparable with the results of the relevant subpopulation as described in research question 1. No further statistically significant effects are shown.

I 4.2.4 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.

The subgroup analyses conducted by the company in Module 4A relate to the total population of the CLARITY AD study. As supplementary information, it presents subgroup analyses for the subpopulation of patients with MCI (subpopulation without consideration of the regulatory requirements) and for the subpopulation of patients with MCI without anti-dementia drugs at baseline (subpopulation without consideration of the regulatory requirements) in Module 4A, Appendix 4-G. However, no subgroup results are available for the relevant subpopulation.

I 4.3 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 IQWiG *General Methods* [1].

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.

I 4.3.1 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 I 4.2.3 (see Table 14).

Determination of the outcome category for the outcome infusion-related reaction (AE)

According to the company, the majority of events recorded under this outcome were classified as non-serious or not severe. Although this conclusion refers to the total study population, it can be assumed that this assessment does not deviate significantly in the subpopulations under consideration. Therefore, the outcome was assigned to the outcome category non-serious/non-severe side effects.

Table 14: 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	ND vs. ND[c] RR: – p: –	Lesser benefit not proven/added benefit not proven
Morbidity		
Symptoms (CDR-SB – deterioration at Month 18)	10.2% vs. 11.5% RR: 0.88 [0.52; 1.52]; p = 0.655	Lesser benefit not proven/added benefit not proven
Cognition (ADAS-Cog14 – deterioration at Month 18)	5.2% vs. 5.6% RR: 0.93 [0.42; 2.05]; p = 0.848	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: 1.04 [0.68; 1.58]; p = 0.864	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; 1.79]; p = 0.987	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	ND vs. ND RR: – p: –	Greater/lesser harm not proven
Infusion related reaction (AE)	26.6% vs. 7.8% RR: 3.43 [2.13; 5.53]; RR: 0.29 [0.18; 0.47][d] p < 0.001 probability: hint	Outcome category: non-serious/non-severe side effects $0.80 < CI_u$ greater harm, extent: considerable

Table 14: 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]**
Other specific AEs	No suitable data[e]	Greater/lesser harm not proven

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. Based on the available data on the MCI population without anti-dementia drugs (without consideration of the regulatory requirements), it can be estimated with sufficient certainty that no statistically significant result is to be expected in the relevant subpopulation either.
d. Institute's calculation; reversed direction of effect to enable the use of limits to derive the extent of added benefit.
e. Suitable analyses on AEs are not available; a choice of further specific AEs is therefore impossible.

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

I 4.3.2 Overall conclusion on added benefit

Table 15 summarizes the results taken into account for the overall conclusion on the extent of the added benefit.

Table 15: 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, behavioural changes, symptomatic ARIA events and other specific AEs. No subgroup results are available for the relevant subpopulation.	
AE: adverse event	

For research question 1 of this benefit assessment, a negative effect was shown in the category non-serious/non-severe side effects, based on a specific AE (infusion-related reactions) with considerable extent.

No results are available for symptomatic ARIA events and further specific AEs. Moreover, no subgroup results are available for the relevant subpopulation. In the current data situation, it is not possible to assess the impact of these missing data on the overall assessment. In particular with regard to the lack of results on symptomatic ARIA events, the available results

do not rule out a greater harm. The outcomes independence in everyday life and behavioural changes were not recorded in the study.

Table 8 presents an overview of the missing data for the relevant subpopulation. Furthermore, data and results are missing for other potentially significant subpopulations within the approval population (see also I Appendix F of the full dossier assessment).

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.

The assessment described above deviates from that of the company, which derived proof of considerable added benefit for the total population across research questions.

I 5 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 (see Table 4).

Due to the design of the relevant study, this benefit assessment only allows conclusions regarding the use of lecanemab as add-on therapy to existing AChEI treatment for patients with mild Alzheimer's dementia. Patients with mild Alzheimer's dementia who were not receiving AChEI treatment at baseline were randomized to receive either lecanemab or a placebo. For these patients, there is no comparison with the ACT. No reasons have been given as to why patients with mild Alzheimer's dementia were not treated with AChEIs in the study. Patients with mild Alzheimer's dementia for whom treatment with AChEIs is not, or is no longer, an option (e.g. due to lack of efficacy, contraindications, unacceptable side effects or the patient's request) are not covered by the G-BA's research questions.

I 5.1 Study characteristics (specific to research question 2)

For characteristics of the studies that apply to all research questions, see Section I 3.2.

I 5.1.1 Patient characteristics

Table 16 shows the characteristics of the patients in the subpopulation of the included study relevant for research question 2.

Table 16: 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] = 139**	**Placebo + AChEI N[a] = 138**
CLARITY AD		
Age [years], mean (SD)	ND	ND
Sex [F/M], %	ND	ND
Region (IxRS), n (%)	ND	ND
ApoE ε4 carrier status by genotype (laboratory), n (%)		
Heterozygotes	ND	ND
Non-carriers	ND	ND
CDR-GS		
0.5 (very mild dementia)	ND[b]	ND[b]
1 (mild dementia)	ND[b]	ND[b]
CDR-SB	N[c] = 136	N[c] = 137
Mean (SD)	3.7 (1.29)	3.7 (1.38)
Median [Q1; Q3]	ND	ND
MMST	ND	ND
ADAS-Cog14	N[c] = 136	N[c] = 137
Mean (SD)	27.3 (6.86)	26.9 (7.90)
Median [Q1; Q3]	ND	ND
EQ-5D VAS	N[c] = 136	N[c] = 137
Mean (SD)	83.9 (11.87)	80 (14.97)
Median [Q1; Q3]	ND	ND
QOL-AD	N[c] = 136	N[c] = 137
Mean (SD)	39.3 (6.06)	38.3 (6.47)
Median [Q1; Q3]	ND	ND
Age at initial onset of symptoms [years], n (%)	ND	ND
Age group at initial onset of symptoms [years], n (%)	ND	ND
Time since initial onset of symptoms [years], mean (SD)	ND	ND
Age at diagnosis [years], n (%)	ND	ND
Age group at diagnosis [years], n (%)	ND	ND
Time since diagnosis [years], n (%)	ND	ND
Treatment discontinuation, n (%)	ND	ND
Study discontinuation, n (%)	ND	ND

Table 16: 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] = 139	Placebo + AChEI N[a] = 138

a. Number of randomized patients who received at least one dose of the respective treatment. Values that are based on other patient numbers are marked in the corresponding column if the deviation is relevant.
b. In the subpopulation of patients with mild Alzheimer's dementia (without consideration of treatment at baseline and regulatory requirements), 50% vs. 50% had a CDR-GS of 0.5, whilst 49% vs. 51% had a CDR-GS of 1.0 in the intervention arm versus the control arm; Institute's calculation.
c. Number of randomized 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; data on baseline values for the respective instruments.

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 company does not provide any information on the characteristics of the study population for the relevant subpopulation. It is possible to derive individual data on values at the time of randomization from the results for outcomes that are analysed on a continuous basis. The characteristics of patients with mild Alzheimer's dementia with AChEI therapy but without consideration of the ApoE ε4 carrier status and the use of anticoagulants at baseline are set out in the appendix (see Table 24). Taking these details into account, the patients in the relevant subpopulation are described in more detail below.

The mean age of the patients was around 70 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 a few years before they reached the age of 70.

At the start of the study, patients in the relevant subpopulation had a CDR-SB of 3.7. Given a scale range of 0 to 18, this score corresponds to the stage of very mild dementia (see also I Appendix E.2 of the full dossier assessment). 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, which measure quality of life in people with Alzheimer's disease, averaged 39 and 38 respectively on a scale ranging from 13 to 52, with higher scores indicating a better quality of life. Further details on the instruments mentioned are set out in Section I 4.2.1. 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.

Moreover, there are no data on treatment discontinuation for the relevant subpopulation. In the population with mild Alzheimer's dementia with AChEI therapy (without consideration of the regulatory requirements), more patients in the intervention arm discontinued treatment prematurely than in the control arm (23% vs. 15%; see also Table 24). Common reasons for treatment discontinuation were AEs, withdrawal of consent and patient decision. There was no information on study discontinuations for the relevant subpopulation. The data in the study report show that, in the total population, the majority of patients who discontinued treatment (22% vs. 17%) also discontinued the study (19% vs. 16%).

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

Comparison of patient characteristics of the populations with MCI (research question 1) and mild Alzheimer's dementia (research question 2)

Compared with the MCI population, patients with mild Alzheimer's dementia have a CDR-SB score that is approximately 1 point higher (approx. 3.7 vs. approx. 2.6) and an ADAS-Cog14 score that is 5 points higher (approx. 27 vs. approx. 22). Both increases are generally associated with a higher degree of severity (see Table 9 and Table 16). However, according to the CDR-SB staging system, the patients in the subpopulation for research question 2 did not yet fall within the mild Alzheimer's dementia category. The scores on the EQ-5D VAS (approx. 82) and QOL-AD (approx. 39) are comparable between the populations with MCI and mild Alzheimer's dementia. Compared with patients with MCI, patients with mild Alzheimer's dementia have a slightly longer period since diagnosis (approximately half a year longer) and since the occurrence of the first symptoms (approximately half a year longer) (see Tables 21 and 24 in I Appendix C of the full dossier assessment).

The mean age is the same; there are slightly more women in the population with MCI due to Alzheimer's disease.

Concomitant treatments

In accordance with the study's inclusion criteria, the concomitant anti-dementia treatment had to have been maintained at a stable dose for at least 12 weeks prior to baseline (see also Section I 3.2.1). It is unclear to what extent, as part of the study inclusion (e.g. 12 weeks before baseline) changes to the therapy (discontinuation or initiation) were still being made with a view to treatment optimization or review of the diagnosis. Information on the duration of prior treatment was requested but is not available. Only patients with mild Alzheimer's dementia and AChEI treatment at baseline were included for research question 2. Changes to concomitant therapy were to be avoided, although they were permitted where medically necessary.

Concomitant therapies at baseline and during the course of the study are set out in Table 25 of I Appendix C.2 of the full dossier assessment for the population with mild Alzheimer's dementia with AChEI therapy (subpopulation without consideration of the regulatory requirements). During the course of the study, concomitant therapies were adjusted in 10% and 16% of patients in the both study arms respectively; the majority of these patients in both arms received donepezil treatment during the course of the study (see also the section 'Lack of guidelines on how to deal with lack of efficacy or progression to the next stage' in Section I 3.2.3.3). 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, there is no information on the dosage (see also Section I 3.2.3.3).

I 5.1.2 Risk of bias across outcomes (study level)

The risk of bias across outcomes (risk of bias at study level) is described in Table 10 in Section I 4.1.2 and was rated as low for the study.

I 5.1.3 Transferability of the study results to the German health care context

The company's assessment regarding the transferability of the study results to the German health care context is described in Section I 4.1.3.

For the transferability of the study results, see also Sections I 3.2.2.1 and I 3.2.2.1.

I 5.2 Results on added benefit

I 5.2.1 Outcomes included

The patient-relevant outcomes that were to be included in the assessment were identical for research questions 1 and 2 and can be found in Section I 4.2.1. The matrix of outcomes presented in Section I 4.2.1 (Table 11) shows for which outcomes data were available in the included study.

I 5.2.2 Risk of bias

The outcome-specific risk of bias did not differ between research question 1 and research question 2 and can therefore be found in Section I 4.2.2. The additional aspects relating to the certainty of conclusions, as set out in Section I 4.2.2, must also be taken into account. Based on the CLARITY AD study, at most hints, e.g. of an added benefit, could therefore be determined for all outcomes presented, also for research question 2, after assessment of the certainty of conclusions.

I 5.2.3 Results

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. Where necessary, calculations conducted by the Institute are provided in addition to the data from the company's dossier.

Tables on common AEs, common SAEs and discontinuations due to AEs are presented in I Appendix H.2 of the full dossier assessment.

Table 17: Results (mortality, morbidity, health-related quality of life, side effects) – 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]		ND[b]		ND[b]	ND[c]
Morbidity					
Symptoms (CDR-SB – deterioration at Month 18[d])	103	28 (27.2)	115	39 (33.9)	0.80 [0.53; 1.20]; 0.286[e]
Cognition (ADAS-Cog14 – deterioration at Month 18[f])	99	14 (14.1)	111	26 (23.4)	0.60 [0.33; 1.09]; 0.094[e]
Independence in everyday life				No suitable data[g]	
Behavioural changes				No suitable data[g]	
Health status (EQ-5D VAS – improvement at Week 18[h])	103	16 (15.5)	113	25 (22.1)	0.70 [0.40; 1.24]; 0.222[e]
Health-related quality of life					
QOL-AD – deterioration at Month 18[i])	104	10 (9.6)	113	19 (16.8)	0.57 [0.28; 1.17]; 0.127[e]
Side effects					
AEs (supplementary information)[j]	139	127 (91.4)	138	111 (80.4)	–
SAEs[j]	139	20 (14.4)	138	14 (10.1)	1.42 [0.75; 2.69]; 0.293[k]
Discontinuation due to AEs	139	10 (7.2)	138	4 (2.9)	2.48 [0.80; 7.73]; 0.126[k]
Symptomatic ARIA events		ND[l]		ND[l]	ND[l]
Infusion related reactions (AE)[m]	139	32 (23.0)	138	10 (7.2)	3.18 [1.63; 6.21]; < 0.001[k]
Other specific AEs				No suitable data[n]	

Table 17: Results (mortality, morbidity, health-related quality of life, side effects) – 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. Data for the relevant subpopulation are not available; in the subpopulation of patients with mild Alzheimer's dementia with AChEI therapy (without consideration of the regulatory requirements), there was 1 death in the lecanemab arm and 1 death in the placebo arm. c. Based on the available data on the population with mild Alzheimer's disease with AChEI therapy (without consideration of the regulatory requirements), it can be estimated with sufficient certainty that no statistically significant result is to be expected in the relevant subpopulation either. 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). Further interpretation of the data is impossible due to the lack of information on the domains and distributions for the relevant subpopulations. e. Unstratified logistic regression model. f. 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). g. See Section I 4.2.1of the present dossier assessment for the reasoning. h. 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). i. 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). j. Excluding disease-related events (see Section I 4.2.1). k. Institute's calculation, unconditional exact test (CSZ method according to [66]). l. No data are available for the relevant subpopulation; results for other populations are presented as supplementary information in I Appendix G of the full dossier assessment. m. Operationalized via a PT list compiled by the company. n. No suitable analyses on AEs available, a choice of further specific AEs is therefore impossible. 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; 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			

Based on the available information, at most hints, e.g. of an added benefit, could be determined for all outcomes (see Section I 4.2.2).

Mortality

All-cause mortality

There are no data on deaths during the course of the study for the relevant subpopulation. Based on the available data on the population with mild Alzheimer's disease with AChEI therapy (subpopulation without consideration of the regulatory requirements), it can be estimated with sufficient certainty that no statistically significant result is to be expected in

the relevant sub-population either. 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, but no clinically relevant difference between the treatment groups (see Table 28 and Figure 6 in I Appendix E.1 of the full dossier assessment).

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.

Independence in everyday life

No suitable data were available for the outcome independence in everyday life (see Section I 4.2.1 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 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.

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.

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

There are no data on symptomatic ARIA events during the course of the study for the relevant subpopulation. There was no hint of greater or lesser harm from lecanemab + AChEI in comparison with AChEI; an added benefit is therefore not proven. However, based on the results from other populations, greater harm from lecanemab compared with AChEI cannot be ruled out (see Table 29 in I Appendix G of the full dossier assessment).

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.

Other specific AEs

No suitable data were available for further specific AEs (see Section I 4.2.1 for reasoning). There was no hint of greater or lesser harm from lecanemab + AChEI in comparison with AChEI; greater or lesser harm is therefore not proven.

Results for the pooled subpopulation for research question 1 and research question 2

The pooled results for the population relating to research questions 1 and 2 are presented in I Appendix D of the full dossier assessment as supplementary information. The results of this largest possible population under consideration of the requirements of the marketing authorization and the ACT are comparable with the results of the subpopulation relevant to the assessment as described in research question 2. No further statistically significant effects are shown.

I 5.2.4 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.

The subgroup analyses conducted by the company in Module 4A relate to the total population of the CLARITY AD study. In Module 4A, Appendix 4-G, it presents subgroup analyses for the subpopulation of patients with mild Alzheimer's dementia (without consideration of the ApoE ε4 carrier status or the use of concomitant anti-dementia therapies and anticoagulants at baseline), as well as for the subpopulation of patients with mild Alzheimer's dementia with AChEI therapy (without consideration of the ApoE ε4 carrier status or the use of anticoagulants at baseline). However, no subgroup results are available for the relevant subpopulation.

I 5.3 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 IQWiG *General Methods* [1].

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.

I 5.3.1 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 I 5.2.3 (Table 18).

Determination of the outcome category for the outcome infusion-related reaction (AE)

According to the company, the majority of events recorded under this outcome were classified as non-serious or not severe. Although this conclusion refers to the total study population, it can be assumed that this assessment does not deviate significantly in the subpopulations under consideration. 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	ND vs. ND[c] RR: – p: –	Lesser benefit not proven/added benefit not proven
Morbidity		
Symptoms (CDR-SB – deterioration at Month 18)	27.2% vs. 33.9% RR: 0.80 [0.53; 1.20]; p = 0.286	Lesser benefit not proven/added benefit not proven
Cognition (ADAS-Cog14 – deterioration at Month 18)	14.1% vs. 23.4% RR: 0.60 [0.33; 1.09]; p = 0.094	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: 0.70 [0.40; 1.24]; p = 0.222	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: 0.57 [0.28; 1.17]; p = 0.127	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	ND vs. ND RR: – p: –	Greater/lesser harm not proven
Infusion related reaction (AE)	23.0% vs. 7.2% RR: 3.18 [1.63; 6.21]; RR: 0.31 [0.16; 0.61][d] p < 0.001 probability: hint	Outcome category: non-serious/non-severe side effects $0.80 < CI_u$ greater harm, extent: considerable
Other specific AEs	No suitable data[e]	Greater/lesser harm not proven

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]
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. Based on the available data on the population with mild Alzheimer's dementia with AChEI therapy (without consideration of the regulatory requirements), it can be estimated with sufficient certainty that no statistically significant result is to be expected in the relevant subpopulation either. d. Institute's calculation; reversed direction of effect to enable the use of limits to derive the extent of added benefit. e. No suitable analyses on AEs available, a choice of further specific AEs is therefore impossible. 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		

I 5.3.2 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 ▪ infusion related reaction (AE): hint of greater harm – extent "considerable"
No suitable data are available for the outcomes independence in everyday life, behavioural changes, symptomatic ARIA events and other specific outcomes.	
AChEI: acetylcholinesterase inhibitors; AE: adverse event	

For research question 2 of this benefit assessment, a negative effect was shown in the category non-serious/non-severe side effects, based on a specific AE (infusion-related reactions) with considerable extent.

No results are available for symptomatic ARIA events and further specific AEs. Moreover, no subgroup results are available for the relevant subpopulation. In the current data situation, it is not possible to assess the impact of these missing data on the overall assessment. In particular with regard to the lack of results on symptomatic ARIA events, the available results

do not rule out a greater harm. The outcomes independence in everyday life and behavioural changes were not recorded in the study.

Table 8 provides an overview of the missing data and results for the relevant subpopulation. Furthermore, data and results are missing for other, potentially significant subpopulations within the approval population (see also I Appendix F of the full dossier assessment).

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

There are no suitable data available for comparing lecanemab as monotherapy with AChEI therapy as the ACT in patients with mild Alzheimer's dementia. There was no hint of an added benefit of lecanemab in comparison with the ACT for these patients. An added benefit is therefore not proven.

The assessment described above deviates from that of the company, which derived proof of considerable added benefit for the total population across research questions.

I 6 Probability and extent of added benefit – summary

Table 20 summarizes the result of the assessment of the added benefit of lecanemab in comparison with the ACT.

Table 20: Lecanemab – probability and extent of added benefit

Research question	Therapeutic indication	ACT[a]	Probability and extent of added benefit
Therapeutic indication: 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]	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 ongoing AChEI therapy: 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. 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 drugs used are to be applied in accordance with the marketing authorization within the context of a study.
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 approach for the derivation of an overall conclusion on added benefit is a proposal by IQWiG. The G-BA decides on the added benefit.

I 7 References for English extract

Please see full dossier assessment for full reference list.

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

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