

Donanemab (early Alzheimer's disease)

Addendum to Project A25-134
(dossier assessment)¹

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List of abbreviations

Abbreviation	Meaning
AChEI	acetylcholinesterase inhibitor
ACT	appropriate comparator therapy
ADAS-Cog	Alzheimer's Disease Assessment Scale-Cognitive subscale
ADAS-Cog13	Alzheimer's Disease Assessment Scale-Cognitive subscale 13-item version
ADCS-iADL	Alzheimer's Disease Cooperative Study-instrumental Activities of Daily Living subscale
AkdÄ	Arzneimittelkommission der deutschen Ärzteschaft (Drug Commission of the German Medical Association)
ApoE ε4	apolipoprotein E ε4
ARIA	amyloid-related imaging abnormalities
ARIA-E	amyloid related imaging abnormality-oedema/effusion
ARIA-H	amyloid related imaging abnormality-microhaemorrhages and haemosiderin deposits
CDR	Clinical Dementia Rating
CDR-GS	Clinical Dementia Rating-Global Score
CDR-SB	Clinical Dementia Rating-Sum of Boxes
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
iADRS	Integrated Alzheimer's Disease Rating Scale
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
MCI	mild cognitive impairment
MedDRA	Medical Dictionary for Regulatory Activities
MMSE	Mini-Mental State Examination
mSAF	modified safety analysis set
PT	Preferred Term
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
SMQ	Standardized MedDRA Query

1 Background

On 10 March 2026, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to conduct supplementary assessments for Project A25-134 (Donanemab – Benefit assessment according to §35a Social Code Book V) [1].

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

- Assessment (evaluation of suitability and, where applicable, presentation) of the analyses relating to the subpopulations identified during the commenting procedure, using additional differentiation criteria based on the Mini-Mental State Examination (MMSE), the Clinical Dementia Rating-Global Score (CDR-GS) and the Clinical Dementia Rating-Sum of Boxes (CDR-SB)
- Inclusion of the subsequently submitted data on the dose distribution of donanemab during the course of the study (modified safety analysis set [mSAF] total population)

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

2 Assessment

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

Table 1: Research questions for the benefit assessment of donanemab

Research question	Therapeutic indication	ACT ^a
Adults with early Alzheimer's disease with confirmed amyloid pathology who are ApoE ε4 non-carriers or heterozygotes:		
1	with clinically diagnosed MCI due to Alzheimer's disease	watchful waiting ^b
2	with clinically diagnosed 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. The AChEIs (donepezil, galantamine and rivastigmine) are approved for the symptomatic treatment of mild to moderate Alzheimer's dementia. The aim should be to administer the highest tolerable dose. For the benefit assessment, the on-label use of drugs within the context of a study must be observed. AChEI: acetylcholinesterase inhibitor; ACT: appropriate comparator therapy; ApoE ε4: apolipoprotein E ε4; G-BA: Federal Joint Committee; MCI: mild cognitive impairment		

The randomized controlled trial (RCT) AACI was included for the benefit assessment of donanemab compared with the appropriate comparator therapy (ACT) in adult patients with clinically diagnosed mild cognitive impairment (MCI) or mild dementia due to Alzheimer's disease (collectively referred to as early Alzheimer's disease) with confirmed amyloid pathology who are apolipoprotein E ε4 (ApoE ε4) non-carriers or heterozygotes. A detailed description of the study can be found in benefit assessment A25-134 [1].

The subpopulations defined by the company in Module 4 A solely on the basis of treatment with acetylcholinesterase inhibitors (AChEIs) were not suitable for addressing the research questions of the benefit assessment (for a detailed explanation, see A25-134 [1]). In its comments, the company presented further subpopulations for which it applied various differentiation criteria in addition to the treatment. Queries regarding the data were addressed by the company following the oral hearing [2]. This addendum covers the assessment of all the data made available.

2.1 Limitations of the AACI study

The following limitations were described in the dossier assessment A25-134 (for details, see A25-134):

- Duration of study with limited informative value

- Uncertainties regarding the population
- Uncertainties regarding intervention and concomitant therapy

With regard to one of the uncertainties concerning the intervention and concomitant therapy – namely, deviations from the administration of donanemab as set out in the summary of product characteristics (SmPC) – the company provided details in its comments on the dosing of donanemab during the course of the study. In the Module 4 A total population (mSAF population), 92% of patients received the 1400 mg dose specified in the SmPC following the titration phase [2,4]. The data show that the dose was largely reduced to 0 mg where necessary during the course of the study, which is also provided for in the SmPC under certain circumstances. Consequently, for only a small proportion of the Module 4 A total population in the AACI study was the dose reduced to 700 mg rather than the treatment being discontinued entirely, which is not provided for in the SmPC. No data were available on the company's subpopulations from Module 4 A or the subpopulations referred to in the comments.

In particular, there was still no information available on dosage, the drugs used or modifications to the AChEI treatment. Furthermore, no information was available on non-drug treatments or on how to deal with a lack of efficacy or progression to the next stage. For both research questions, therefore (regardless of the suitability of the data provided), uncertainties remained regarding the implementation of the ACT.

2.2 Subpopulations presented by the company

For the benefit assessment, the company had initially submitted 2 subpopulations from the AACI study in Module 4 A in relation to the G-BA's 2 research questions. To form the subpopulations, the company used the original analysis population from the AACI study, excluded from this the homozygous ApoE ε4 carriers, who are not within the approved therapeutic indication for donanemab [4], and finally excluded patients receiving memantine treatment. The company then filtered the resulting Module 4 A total population into a 'subpopulation a1' comprising patients not receiving AChEI treatment at screening. This subpopulation without AChEI treatment was presented by the company for research question 1 of the benefit assessment (patients with clinically diagnosed MCI due to Alzheimer's disease). In addition, the company filtered the Module 4 A total population into a 'subpopulation a2' of patients receiving AChEI treatment (treatment with donepezil, rivastigmine or galantamine) at screening. The subpopulation receiving AChEI treatment was presented by the company for research question 2 of the benefit assessment. As the rationale for dividing the population into subpopulations for the 2 benefit assessment research questions based solely on patients' treatment status at screening (AChEI treatment versus no AChEI treatment), the company cited in Module 4 A fluid transitions between disease stages, which depend on many patient-specific factors, such as personal ability, habits, living

circumstances and coping mechanisms, as well as information provided by relatives and, ultimately, the physician's assessment. In its reasoning regarding the insufficient distinguishability of the stages of Alzheimer's disease, the company also emphasized, with reference to the S3 guideline dated 28 March 2025, that the use of a single measurement instrument (e.g. the MMSE) is not recommended for distinguishing between MCI and mild dementia caused by Alzheimer's disease. In Module 4 A, the company also stated that the scores obtained from individual instruments within a clinical study are not suitable for distinguishing between disease stages, as they are difficult to interpret without knowledge of the longitudinal course of the disease and are additionally influenced by any prior treatment with antidementia drugs. Dossier assessment A25-134 described why splitting the study population by treatment (untreated or receiving AChEI treatment) does not result in the division of the study population by diagnosis (MCI or mild Alzheimer's dementia).

In its comments, the company presented 3 further subpopulations for each of the 2 benefit assessment research questions. Based on the subpopulations presented in Module 4 A, split according to AChEI treatment, it used cut-off values on the MMSE and Clinical Dementia Rating (CDR) scales to form populations divided into MCI and mild Alzheimer's dementia (see Figure 1).

Company's approximation of research question 1			Company's approximation of research question 2		
without AChEI N: 284 vs. 270	without AChEI N: 284 vs. 270	without AChEI N: 284 vs. 270	with AChEI N: 277 vs. 291	with AChEI N: 277 vs. 291	with AChEI N: 277 vs. 291
	without AChEI and CDR-GS 0.5 N: 205 vs. 187	without AChEI and CDR-SB 0.5 – 4.0 N: 202 vs. 186	with AChEI and MMSE 20-26 N: 249 vs. 246		
without AChEI and MMSE 27 - 30 N: 77 vs. 53				with AChEI and CDR-GS 1 or 2 N: 122 vs. 110	with AChEI and CDR-SB 4.5 - 9 N: 119 vs. 107

AChEI: acetylcholinesterase inhibitor; CDR-GS: Clinical Dementia Rating-Global Score; CDR-SB: Clinical Dementia Rating-Sum of Boxes; MMSE: Mini-Mental State Examination; N: number of patients

Figure 1: Graphical representation of the populations from the company's comments

As already described in the dossier assessment, the AChEI treatment status is not suitable as an indicator for a clinical diagnosis distinguishing between MCI and mild Alzheimer's dementia. The AACI study did not define any inclusion criteria for distinguishing between MCI and mild Alzheimer's dementia. Both the S3 guideline of 28 March 2025 and the current S3 guideline recommend treatment with AChEIs from the stage of mild dementia onwards, and

not as early as the stage of MCI due to Alzheimer's disease [5]. However, it is known from the lecanemab assessment that a relevant proportion of patients with MCI receive off-label AChEI treatment. Furthermore, the Drug Commission of the German Medical Association (AkdÄ) points out that different codes are used for MCI and mild Alzheimer's dementia under the International Statistical Classification of Diseases and Related Health Problems, 10th Revision (ICD-10) [6].

However, filtering by treatment is appropriate in that, given the placebo-controlled study design, for research question 1 the ACT only allows patients not receiving AChEI treatment to be considered; and for research question 2 the ACT only allows patients receiving AChEI treatment to be considered. In order to represent populations with MCI or mild Alzheimer's dementia, the company provided an additional breakdown based on threshold values on the MMSE or CDR scales. A presentation of disease-related patient characteristics for the subsequently included subpopulations can be found in Appendix A. However, this breakdown based on a single scale in combination with supportive therapy does not necessarily provide an adequate approximation of the populations under consideration in the research questions. This is justified in the following sections.

Limitations of the subpopulations presented

The characteristics of the subsequently submitted subpopulation suggested that, as a result of the additional disease-specific scales taken into account, the proportion of incorrectly classified patients (i.e. an MCI population in research question 2 or a population with mild Alzheimer's dementia in research question 1) was reduced in the newly available populations (see Appendix A and also Figure 2). Nevertheless, the populations made available could, at best, serve as an approximation of the populations relating to research question 1 and research question 2 respectively. The current German S3 guideline [5] recommends that a diagnosis of mild cognitive impairment should be made on the basis of clinical findings and neuropsychological evidence of cognitive impairment, provided the patient's everyday competence remains fully or largely intact and complete independence is retained. According to the guideline, mild cognitive impairment is defined in principle as a syndrome characterized by the presence of objective cognitive impairments which represent a decline from an unaffected baseline, but which are not severe enough to impact on the ability to live independently. It states that impairment to complex everyday functions is consistent with a diagnosis of mild cognitive impairment. The guideline also says that various neuropsychological criteria are available for identifying an 'objectifiable cognitive impairment', which make it possible to distinguish between MCI and normal cognitive function. However, for this benefit assessment and to address its research questions, it is necessary not only to distinguish between the condition and normal cognitive function, but also, in particular, to distinguish it from mild Alzheimer's dementia. According to the current S3 guideline [5], a diagnosis of dementia requires, in addition to neuropsychological tests,

functional impairments to everyday activities as a key criterion; these are to be determined through the patient's personal and third-party medical history. Various scales are simply listed in a table in the appendix without any specific cut-off values.

With its comments, the company submitted subpopulations according to AChEI treatment in combination with MMSE or CDR scale scores (in the form of CDR-GS or CDR-SB).

Division according to MMSE scores

The MMSE has a scale range of 0 to 30 points. To represent the population with MCI, the company used a score range from 27 to 30. To represent the population with mild Alzheimer's dementia, the company used a score range from 20 to 26. It used cut-off values specified in the guideline as an orientation for rating the severity of dementia. The guideline describes the MMSE as a widely used scale that can be employed as part of a clinical assessment of cognitive impairment and functional impairment [5]. The MMSE is described as a brief test for use in general practice, which is suitable for objectively assessing cognitive impairment, but is only an indicative screening tool. The MMSE is therefore not suitable for distinguishing between MCI and mild dementia. Furthermore, the MMSE only represents cognition and is therefore not suitable for categorization whilst taking into account retained everyday competence. The use of this scale to distinguish between MCI and mild Alzheimer's dementia within the study population was therefore assessed as not appropriate.

Division according to scores in CDR-GS or CDR-SB

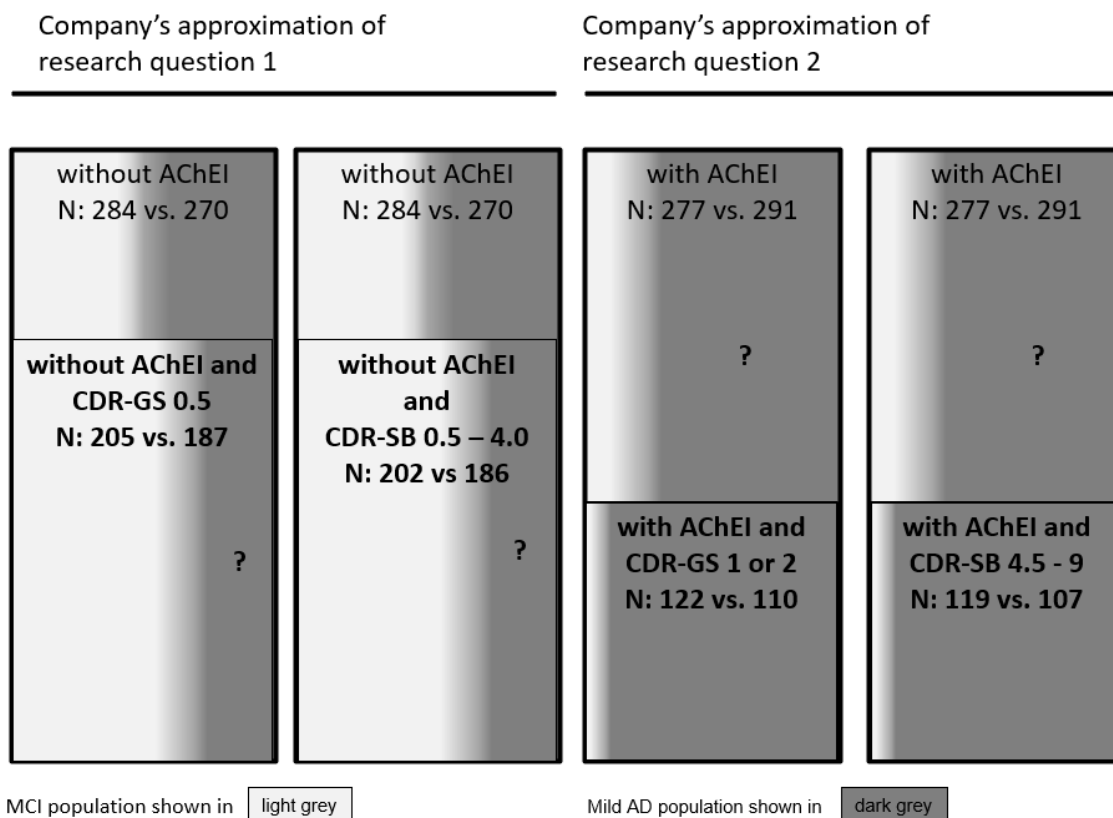
The CDR is mentioned in the guideline as one of the methods for recording the severity of dementia. However, the guideline does not assign a prominent role to the CDR in general, or to the CDR-GS or CDR-SB in particular, in distinguishing between MCI and mild dementia. As outlined above, according to the guideline various neuropsychological criteria are available for the diagnosis of an objectifiable cognitive disorder, which enable a distinction to be made between MCI and normal cognitive function. However, the diagnosis of MCI also requires it to be distinguished from mild dementia and is based on clinical findings and neuropsychological evidence of a cognitive impairment while the patient's everyday competence remains fully or largely intact and complete independence is retained. The CDR is analysed as a sum score (CDR-GS or CDR-SB) and comprises the categories of cognition and everyday activities, each of which has 3 domains. During the commenting procedure, the CDR-GS in particular was described as a scale established in clinical practice for diagnostic purposes [2]. However, in the algorithm used to determine the CDR-GS, the 'memory' domain is of particular importance, whereas in the determination of the CDR-SB, all domains are weighted equally, meaning that the 'everyday activities' domain is potentially more taken into account. However, when categorizing patients according to CDR sum scores, it cannot be concluded with certainty that patients with largely retained everyday competence will be included in the

MCI subpopulation, whilst patients with more severe impairments to everyday competence will be included in the subpopulation with mild dementia.

Thus, the cut-off values used by the company for the CDR-SB correspond to the ranges of scores associated with MCI (scores from 0.5 to 4.0) and mild dementia (scores from 4.5 to 9.0) respectively [7,8]. The CDR-SB is calculated by adding together the scores in the individual domains (see Figure 3 in Appendix B). It is possible to achieve a score of 4.5 even where the impact on daily life is questionable. On the other hand, with a moderate impact on daily life, a score of 4 may be recorded.

For the CDR-GS, the company used a score of 0.5 to represent the MCI population and a score of 1 or 2 to represent the population with mild Alzheimer's dementia. It did not explain why patients with a score of 2 were included in the CDR-GS. A score of 2 is associated with moderate dementia and was also used by the company to represent a transition to the moderate stage. The CDR-GS is calculated using an algorithm in which the 'memory' subdomain is given extra weight [9]. In line with the comments above regarding CDR-SB, even a CDR-GS score of 0.5 may point to relevant limitations in everyday activities (see Figure 4 in Appendix B). This was also confirmed during the oral hearing in response to specific questions from clinicians, where it was pointed out that a sum score does not allow for reliable conclusions to be drawn about the scores in the individual domains [10]. Furthermore, data from the CLARITY AD study showed that around half of patients with mild Alzheimer's dementia had a CDR-GS of 0.5 [11].

Figure 2 represents the subpopulations formed by the company based on CDR-GS and CDR-SB cut-off values, as well as a graphical representation of the population with mild Alzheimer's dementia in research question 1 and the potentially included MCI population in research question 2.



The ‘?’ symbols show important uncertainties regarding the populations, which, on the one hand (research question 1), are attributable to the fact that (untreated) patients with a CDR-GS of 0.5 or a CDR-SB of 0.5 to 4.0 may already exhibit relevant impairment to everyday competence and would therefore be categorized as belonging to the population with mild Alzheimer’s dementia. On the other hand (research question 2), the CDR-GS 1 or 2 and CDR-SB 4.5 to 9 populations did not include potentially relevant patients with mild Alzheimer’s dementia who, despite a CDR-GS of 0.5 or a CDR-SB of 0.5 to 4.0, already exhibit relevant limitations in their daily lives and receive treatment with AChEIs in accordance with the ACT. This is explained in Sections 2.3.1 and 2.4.1 respectively.

AChEI: acetylcholinesterase inhibitor; ACT: appropriate comparator therapy; AD: Alzheimer’s dementia; CDR-GS: Clinical Dementia Rating-Global Score; CDR-SB: Clinical Dementia Rating-Sum of Boxes; MCI: mild cognitive impairment; N: number of patients

Figure 2: Subpopulations based on CDR-GS and CDR-SB cut-off values, and a graphical representation of the potentially included populations with MCI / mild Alzheimer’s dementia

The extent to which the populations formed based on CDR cut-off values could be used for benefit assessment purposes is explained below, separately for each research question.

2.3 Research question 1

Research question 1 considers the patient population of adult patients with clinically diagnosed MCI due to Alzheimer's disease without AChEI treatment at baseline who are ApoE ε4 non-carriers or heterozygotes (see Table 1).

2.3.1 The populations presented do not represent a population of untreated patients with MCI

The populations presented by the company were not suitable for representing the research question 1 population with sufficient certainty. This is explained below.

The results suggested that a relevant proportion of the population had mild Alzheimer's dementia

The populations formed using a CDR-GS score of 0.5 or a CDR-SB score range of 0.5 to 4.0 show an overlap of 98% (based on CDR-SB) and 97% (based on CDR-GS) [2,3] and were therefore considered together. In order to consider the extent to which these populations might represent a population with diagnosed MCI, comparisons were conducted with the MCI population from the CLARITY AD study. In CLARITY AD, patients were diagnosed using the NIA-AA criteria [12]. The approach described there, which focuses on impairment to everyday activities to distinguish between MCI and mild Alzheimer's dementia, is comparable to the approach set out in the current German guideline [5]. In addition, patients diagnosed with MCI had to have a CDR-GS score of 0.5 to be eligible for inclusion in CLARITY AD. Patients diagnosed with mild Alzheimer's dementia had to have a CDR-GS score of 0.5 or 1 to be eligible for inclusion. The patient characteristics showed that half of patients with mild Alzheimer's dementia had a CDR-GS of 0.5 [11]. However, according to the company's approach, provided they had not received AChEI treatment, these patients were categorized within the subpopulation for research question 1. It could not be assumed that based on a score of 0.5 in the CDR-GS, patients with mild Alzheimer's dementia (not receiving AChEI treatment) had been sufficiently excluded from the population for research question 1. It is important that in CLARITY AD, around one-third of patients with mild Alzheimer's dementia remained untreated, and that similar proportions were discussed in the context of clinical practice.

Furthermore, a comparison of the results of the AACI study with those of CLARITY AD suggested that a high proportion of patients with mild Alzheimer's dementia not receiving AChEI therapy were included in the subpopulation with a CDR-GS of 0.5 or a CDR-SB of 0.5 to 4.0 presented by the company for research question 1. When comparing the proportions of patients in the comparator arms of the company populations defined by CDR-GS scores of 0.5 and CDR-SB of 0.5 to 4.0 with the proportions of patients diagnosed with MCI in CLARITY AD, it is notable that the proportion of patients not receiving AChEI therapy with a deterioration in the CDR-SB by Month 18 (defined as a deterioration of at least 15% [corresponding to 3 points]) in the company populations defined by CDR was at around 22% clearly higher than in the MCI population of CLARITY AD, where the proportion was 11.5% (see Appendix D). By contrast, 26.7% of patients in the CLARITY AD study population had mild Alzheimer's dementia and were not receiving AChEI treatment. The proportion of over 20% of patients in the AACI study with a relevant deterioration after 18 months without treatment thus points to a high proportion of patients with mild Alzheimer's disease without AChEI treatment. Furthermore,

when comparing the proportions of patients with deterioration in the comparator arms for both research questions, it is notable that, overall, the proportion of patients with deterioration in the AACI study – at almost 30% – was clearly higher than in the CLARITY AD study at 19.3%. This suggests that there was a generally high proportion of patients with mild Alzheimer’s dementia in the AACI study. It was therefore assumed that a relevant proportion of patients with mild Alzheimer’s dementia without AChEI treatment were included in the populations presented by the company for research question 1, based on their AChEI treatment status and CDR score. Data from the CLARITY AD study showed that the effect estimate for the subpopulation of patients with mild Alzheimer’s dementia without AChEI treatment (relative risk = 0.55) may bias the effect estimate for the subpopulation relating to research question 1 (relative risk = 0.85) in favour of the intervention (see Appendix C). It was unclear why these patients remained untreated. There was also no information available for the AACI study regarding the reasons for treatment or non-treatment with AChEIs.

Systematic bias

In its comments, the company pointed out that the results for the subsequently submitted subpopulations were consistent for both research questions and were consistent, in terms of the effect direction and effect sizes, with the definitions of the subpopulations in Module 4 A based solely on AChEI treatment [2]. The new filtering criteria yielded results that were partly comparable with one another (see Appendix A and [3]) and with the subpopulations in Module 4 A [13], particularly in the company’s subpopulations without AChEI treatment. However, it was possible to explain this by the comparable filtering of the subpopulations according to AChEI treatment and scales that include a cognitive domain not relevant to differentiation; it may therefore also suggest that both populations included a relevant proportion of patients with mild Alzheimer’s dementia without AChEI treatment. The consistent results may therefore have been due to a systematic bias in the same direction, favouring the intervention. It should also be noted that the CDR-GS and the CDR-SB are based on the same assessment tool, the CDR, and are therefore highly correlated. In the supplementary submission, the company stated that the populations split by CDR showed a 94.2% overlap.

Relevance of the untreated mild Alzheimer’s dementia population to the research question 1 population in the context of the available data

As previously explained, the company’s approach – formation of a subpopulation of patients with MCI by using individual scales that are insufficient to distinguish between MCI and mild dementia, combined with filtering based on AChEI treatment – led to a potentially relevant bias in favour of the intervention. The extent to which this might affect the available results was assessed for the key morbidity outcome, the CDR-SB. The company submitted time-to-event analyses for permanent deterioration of $\geq 15\%$, as well as responder analyses of deterioration of $\geq 15\%$ at Week 76. As sensitivity analyses of time-to-event analyses require individual patient data, tipping-point analyses were conducted for the responder analyses.

These were conducted in an unstratified manner, based on the Institute's calculation for the outcome of cognitive decline and deterioration in everyday activities as measured by the CDR-SB at Week 76. As previously explained, the data from CLARITY AD suggested that including a population of patients with mild Alzheimer's dementia without AChEI treatment skews the effect in favour of the intervention. This is due, in particular, to a higher proportion of patients whose condition has deteriorated in the comparator arm (see Appendix C and Appendix D). Excluding these patients and those from the placebo arm by gradually reducing the number of patients, whilst simultaneously and incrementally reducing the number of events, leads to a loss of statistical significance even with as few as 8 patients (4% of the patients in each respective placebo arm of the population with a CDR-GS of 0.5 and CDR-SB of 0.5 to 4.0). Given the likely high proportion of patients with mild Alzheimer's dementia in the study and the likely high proportion of patients with mild Alzheimer's dementia in the subpopulations presented by the company, it was therefore not possible to draw any reliable conclusions regarding research question 1 on the basis of the available results.

Summary

The data submitted by the company during the commenting procedure – relating to 3 populations without AChEI treatment and additionally having an MMSE score of 27 to 30, or a CDR-GS score of 0.5, or a CDR-SB score of 0.5 to 4.0 – were not suitable for research question 1 of the benefit assessment. No suitable data were therefore available. There is no hint of an added benefit of donanemab in comparison with the ACT. An added benefit is therefore not proven.

2.4 Research question 2

Research question 2 considers the patient population of adult patients with clinically diagnosed mild Alzheimer's dementia with AChEI treatment at baseline who are ApoE ε4 non-carriers or heterozygotes (see Table 1).

2.4.1 The populations presented represent a population with mild Alzheimer's dementia receiving AChEI treatment with sufficient reliability

As already explained in Section 2.2, the reduction in the population with AChEI treatment to include only patients with a CDR-GS of 1 or 2 or a CDR-SB of 4.5 to 9.0 does not necessarily represent the population relevant to research question 2. As the populations with a CDR-GS of 1 or 2 and a CDR-SB of 4.5 to 9.0 overlapped by 95% (based on the CDR-SB) and 92% (based on the CDR-GS) [2,3], they were considered together in this report.

Exclusion of patients with mild Alzheimer's dementia

In both populations, a large proportion of patients with AChEI treatment and those with other CDR scores were excluded (see Figure 1). The data in Module 4 A showed that, in the population with AChEI treatment, around 50% had a CDR-GS score of 0.5. It is unclear whether

these patients had MCI or mild Alzheimer’s dementia (see Section 2.2). The data from CLARITY AD showed that a large proportion of patients diagnosed with mild Alzheimer’s dementia may have a CDR-GS of 0.5. These patients, with a CDR-GS of 1 or 2 or a CDR-SB of between 4.5 and 9.0, were not included in the given population, even though they are covered by research question 2.

Inclusion of patients with moderate Alzheimer’s dementia or MCI

As already described in Section 2.3.1, when considered together with the data from CLARITY AD, the data from the AACI study suggested that the population in the AACI study included a higher proportion of patients with mild Alzheimer’s dementia than the CLARITY AD study. The proportion of patients with deterioration in the placebo arm also point to this (see Appendix D). Although it cannot be ruled out that patients may have a CDR-GS of at least 1 or a CDR-SB of at least 4.5 even without any relevant impairment to everyday activities, this seems rather implausible when considering the CDR (see Appendix B) and has not yet been observed to any relevant extent [8]. In contrast to the proportion of patients with mild Alzheimer’s dementia and a CDR-GS of 0.5, the proportion of patients with MCI and a CDR-GS of at least 1 or a CDR-SB of at least 4.5 was therefore assessed as low.

The inclusion of patients with a CDR-GS of 2 in order to represent a population with mild Alzheimer’s dementia is not reasonable. However, the patient characteristics showed that the proportion of patients with a CDR-GS of 2 was less than 10%, both in the population with a CDR-GS of 1 or 2 and in the population with a CDR-SB of 4.5 to 9.0 (see Table 2). Furthermore, patients receiving memantine were excluded from both populations. As memantine has a marketing authorization for use in at least moderate Alzheimer’s dementia, this approach contributed to the exclusion of patients with moderate Alzheimer’s dementia.

Conclusion

The company’s subpopulations with mild Alzheimer’s dementia, formed on the basis of AChEI treatment and a CDR-GS of 1 or 2, or a CDR-SB of 4.5 to 9.0, represent sufficiently appropriate populations for research question 2 given the available data, and were used for the benefit assessment. It should be noted, however, that a potentially large proportion of patients receiving AChEI treatment and with mild Alzheimer’s dementia, who have different CDR scores – in particular a CDR-GS of 0.5 – was not included in the analyses.

2.4.2 Study characteristics

A detailed description of the study can be found in the dossier assessment A25-134 [1].

Patient characteristics (specific to research question 2)

Table 2 shows the characteristics of the patients in the subpopulations considered for research question 2, with AChEI treatment and a CDR-GS score of 1 or 2 or a CDR-SB score of 4.5 to 9 in the AACI study.

Table 2: Characteristics of the study population and study/treatment discontinuation – RCT, direct comparison: donanemab + AChEI vs. placebo + AChEI (multipage table)

Study Characteristic Category	Subpopulation with AChEI + CDR-GS 1 or 2		Subpopulation with AChEI + CDR-SB 4.5 to 9	
	donanemab + AChEI N ^a = 122	placebo + AChEI N ^a = 110	donanemab + AChEI N ^a = 119	placebo + AChEI N ^a = 107
AACI				
Age [years], mean (SD)	73 (6)	74 (6)	73 (6)	74 (6)
Sex [F/M], %	66/34	60/40	68/32	59/41
Family origin, n (%)				
White	108 (89)	103 (94)	105 (88)	101 (94)
Black or African American	2 (2)	0 (0)	2 (2)	0 (0)
Asian	11 (9)	6 (5)	11 (9)	5 (5)
Other	1 (< 1)	1 (< 1)	1 (< 1)	1 (< 1)
Time since symptom onset [years], mean (SD)	4.39 (2.33)	3.81 (1.97)	4.41 (2.31)	3.93 (2.05)
Time since diagnosis of Alzheimer's disease [years], mean (SD)	1.74 (1.78)	1.48 (1.71)	1.80 (1.75)	1.51 (1.62)
MMSE, mean (SD)	20.09 (3.43)	20.35 (3.47)	20.26 (3.41)	20.29 (3.38)
MMSE score, n (%)				
27-30	ND	ND	ND	ND
20-26	ND	ND	ND	ND
CDR-SB, mean (SD)	5.95 (1.52)	5.71 (1.45)	5.72 (1.14)	5.68 (1.26)
CDR-GS, n (%)				
0	0 (0)	0 (0)	0 (0)	0 (0)
0.5	0 (0)	0 (0)	6 (5)	6 (6)
1	112 (92)	106 (96)	109 (92)	99 (93)
2	10 (8)	4 (4)	4 (3)	2 (2)
ADAS-Cog13, mean (SD)	34.31 (8.26)	33.61 (8.05)	33.53 (7.93)	33.39 (8.08)
ApoE ε4 carrier status, n (%)				
ApoE ε4 heterozygotes	72 (59)	63 (57)	74 (62)	61 (57)
ApoE ε4 non-carriers	50 (41)	47 (43)	45 (38)	46 (43)
Amyloid PET imaging at baseline [Centiloids], mean (SD)	103.49 (35.17)	97.81 (33.06)	101.82 (35.07)	97.00 (32.14)
Number of microhaemorrhages at baseline, n (%)				
0	106 (87)	94 (85)	103 (87)	93 (87)
1	13 (11)	12 (11)	13 (11)	11 (10)
2	1 (< 1)	3 (3)	1 (< 1)	2 (2)
3	1 (< 1)	1 (< 1)	1 (< 1)	1 (< 1)
4	1 (< 1)	0 (0)	1 (< 1)	0 (0)

Table 2: Characteristics of the study population and study/treatment discontinuation – RCT, direct comparison: donanemab + AChEI vs. placebo + AChEI (multipage table)

Study Characteristic Category	Subpopulation with AChEI + CDR-GS 1 or 2		Subpopulation with AChEI + CDR-SB 4.5 to 9	
	donanemab + AChEI N ^a = 122	placebo + AChEI N ^a = 110	donanemab + AChEI N ^a = 119	placebo + AChEI N ^a = 107
Any contraindications at baseline, n (%) ^c	12 (10)	10 (9)	12 (10)	9 (8)
Superficial siderosis or vasogenic oedema at baseline, n (%)	2 (2)	3 (3)	2 (2)	2 (2)
Use of anticoagulants at baseline, n (%)	9 (7)	7 (6)	9 (8)	7 (7)
Uncontrolled blood pressure at baseline, n (%)	1 (< 1)	0 (0)	1 (< 1)	0 (0)
Treatment discontinuation, n (%)	48 (39) ^d	27 (25) ^d	44 (37) ^e	28 (26) ^e
Study discontinuation, n (%)	46 (38) ^f	27 (25) ^f	44 (37) ^g	28 (26) ^g
a. Number of randomized patients; values that are based on other patient numbers are marked in the corresponding line if the deviation is relevant. b. Institute's calculation. c. > 4 microhaemorrhages at baseline, superficial siderosis or vasogenic oedema at baseline, uncontrolled blood pressure at baseline, or use of anticoagulants at baseline. d. Common reasons for treatment discontinuation in the intervention arm vs. control arm were the following (percentages based on randomized patients): AEs (11% vs. 5%), patient request (15% vs. 14%). In addition, 2 (2%) vs. 0 of the randomized patients never started treatment. Furthermore, 59% vs. 75% of the patients completed treatment as planned. 5% vs. 1% died during the course of the study. e. Common reasons for treatment discontinuation in the intervention arm vs. control arm were the following (percentages based on randomized patients): AEs (11% vs. 4%), patient request (13% vs. 15%). In addition, 2 (2%) vs. 0 of the randomized patients never started treatment. Furthermore, 61% vs. 73% of the patients completed treatment as planned. 5% vs. 1% died during the course of the study. f. Common reasons for study discontinuation in the intervention arm vs. control arm were the following (percentages based on randomized patients): AEs (8% vs. 5%), patient request (16% vs. 15%). g. Common reasons for study discontinuation in the intervention arm vs. control arm were the following (percentages based on randomized patients): AEs (8% vs. 4%), patient request (15% vs. 16%). AChEI: acetylcholinesterase inhibitor; ADAS-Cog13: Alzheimer's Disease Assessment Scale-Cognitive subscale 13-item version; AE: adverse event; ApoE ε4: apolipoprotein E ε4; CDR-GS: Clinical Dementia Rating-Global Score; CDR-SB: Clinical Dementia Rating-Sum of Boxes; F: female; M: male; MMSE: Mini Mental State Examination; n: number of patients in the category; N: number of randomized patients; ND: no data; PET: positron emission tomography; SD: standard deviation				

The characteristics of patients in the subpopulations considered here were largely comparable across the treatment arms.

Patients with mild Alzheimer's dementia with AChEI treatment and a CDR-GS of 1 or 2, or a CDR-SB of 4.5 to 9.0, were on average 73 and 74 years old respectively; the majority were female and of white family origin. On average, symptoms had begun 3.8 to 4.4 years previously, and the diagnosis had been made 1.5 to 1.8 years earlier. At the start of the study,

patients in the relevant subpopulations had average CDR-SB scores of 5.7 to 6.0. In both the population with a CDR-GS of 1 or 2 and the population with a CDR-SB of 4.5 to 9.0, the proportion of patients with a CDR-GS of 2 was less than 10%. At baseline, the scores on the ADAS-Cog13 assessment scale for Alzheimer's disease were 33 to 34, on a scale ranging from 0 to 85, with higher scores indicating more severe cognitive impairment. At baseline, the mean MMSE scores were 20 in each case, and 8% to 10% of patients had contraindications to donanemab according to the SmPC.

Treatment was discontinued more frequently in the intervention arm than in the comparator arm (39% vs. 25%, and 37% vs. 26%). The most common reasons for treatment discontinuation in the intervention arm were AEs and patient request; the most common reason for treatment discontinuation in the comparator arm was patient request. The majority of patients who discontinued treatment also discontinued the study (38% vs. 25%, and 37% vs. 26%).

Information on dosage, the drugs used or adjustments to AChEI treatment, as well as on non-drugs treatments, remained unavailable. This was taken into account for the assessment of the certainty of conclusions (see Section 2.4.3.2).

Treatment duration and observation period

Table 3 shows the mean and median treatment durations of the patients as well as the mean and median observation periods for individual outcomes.

Table 3: Information on the course of the study – RCT, direct comparison: donanemab + AChEI vs. placebo + AChEI

Study Duration of the study phase Outcome category Outcome	Subpopulation with AChEI + CDR-GS 1 or 2		Subpopulation with AChEI + CDR-SB 4.5 to 9	
	donanemab + AChEI N = 122	placebo + AChEI N = 110	donanemab + AChEI N = 119	placebo + AChEI N = 107
Treatment duration [days]	N = 120	N = 110	N = 117	N = 107
Median [Q1; Q3]	504.0 [255.5; 507.0]	505.0 [477.0; 510.0]	505.0 [281.0; 507.0]	505.0 [397.0; 509.0]
Mean (SD)	388.1 (170.8)	431.0 (150.7)	393.0 (168.4)	427.6 (151.0)
Observation period [days]				
All-cause mortality ^{a, b}	N = 120	N = 110	N = 117	N = 107
Median [min; max]	533.0 [387.0; 539.0]	534.0 [526.0; 540.0]	533.0 [394.0; 538.0]	534.0 [522.0; 540.0]
Mean (SD)	453.4 (144.9)	472.4 (143.3)	454.1 (141.4)	470.1 (142.9)
Morbidity				
Cognition (ADAS-Cog13) ^c	N = 121	N = 110	N = 118	N = 107
Median [Q1; Q3]	531.0 [358.0; 538.0]	533.5 [457.0; 540.0]	532.0 [344.0; 538.0]	533.0 [449.0; 540.0]
Mean (SD)	422.7 (170.4)	453.8 (165.4)	423.2 (170.1)	450.2 (166.3)
Symptoms (CDR-SB) ^c	N = 120	N = 110	N = 117	N = 107
Median [Q1; Q3]	531.5 [351.0; 538.0]	533.0 [452.0; 540.0]	532.0 [344.0; 538.0]	533.0 [449.0; 539.0]
Mean (SD)	421.8 (171.9)	451.3 (165.7)	422.3 (171.5)	446.5 (166.4)
Health-related quality of life (QOL-AD)	ND	ND	ND	ND
Side effects (all AEs) ^b	N = 120	N = 110	N = 117	N = 107
Median [Q1; Q3]	533.0 [387.0; 539.0]	534.0 [526.0; 540.0]	533.0 [394.0; 538.0]	534.0 [522.0; 540.0]
Mean (SD)	453.4 (144.9)	472.4 (143.3)	454.1 (141.4)	470.1 (142.9)
a. All-cause mortality was recorded as fatal AEs. b. Any event occurring during treatment or within 57 days of the last dose of the study medication, but prior to the first visit in the extension phase, was recorded as an AE. c. The observation period is defined as the period from the date of randomization to the last assessment within the 76-week, randomized, double-blind treatment period + 1. AChEI: acetylcholinesterase inhibitor; ADAS-Cog13: Alzheimer's Disease Assessment Scale-Cognitive subscale 13-item version; AE: adverse event; CDR-GS: Clinical Dementia Rating-Global Score; CDR-SB: Clinical Dementia Rating-Sum of Boxes; N: number of randomized/analysed patients; n: number of patients in the category; ND: no data; Q1: 1st quartile; Q3: 3rd quartile; QOL-AD: Quality of life in Alzheimer's disease; RCT: randomized controlled trial; SD: standard deviation				

Patients in the intervention and control arms were treated for an average of 390 and 430 days respectively during the RCT phase of the AACI study. The observation periods for the morbidity

outcomes were comparable across the subpopulations under consideration. In the intervention and control arms, the observation periods for the outcomes symptoms (CDR-SB) and cognition (ADAS-Cog13) were 420 and 450 days respectively. The outcomes of the side effects category and all-cause mortality were observed for an average of 450 and 470 days, respectively, during the RCT phase.

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

Risk of bias across outcomes (study level)

Table 4 shows the risk of bias across outcomes (risk of bias at study level).

Table 4: Risk of bias across outcomes (study level) – RCT, direct comparison: donanemab + AChEI vs. placebo + AChEI

Study	Adequate random sequence generation	Allocation concealment	Blinding		Reporting independent of the results	Absence of other aspects	Risk of bias at study level
			Patients	Treating staff			
AACI	Yes	Yes	Yes	Yes	Yes	Yes	Low
AChEI: acetylcholinesterase inhibitor; RCT: randomized controlled trial							

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

2.4.3 Results on added benefit

2.4.3.1 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-Cog13
 - Independence in daily life
 - Activities of daily living
 - Behavioural changes

- Health-related quality of life
 - Recorded using the Quality of life in Alzheimer’s disease scale (QOL-AD patient-reported version)
- Side effects
 - Serious adverse events (SAEs)
 - Discontinuation due to AEs
 - Symptomatic ARIA events
 - Infusion-related reactions (PT, 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 5 shows for which outcomes data were available in the included study.

Table 5: Matrix of outcomes – RCT, direct comparison: donanemab + AChEI vs. placebo + AChEI

Study	Outcomes											
	All-cause mortality ^a	Symptoms (CDR-SB)	Cognition (ADAS-Cog13)	Independence in daily life	Activities of daily living	Behavioural changes	Health-related quality of life (QOL-AD, patient-reported version)	SAEs	Discontinuation due to AEs	Symptomatic ARIA events ^b (AEs)	Infusion-related reactions ^c (PT, AEs)	Other specific AEs
AACI	Yes	Yes	Yes	No ^d	No ^d	No ^d	No ^e	Yes	Yes	Yes ^f	Yes	No ^g
a. The results on all-cause mortality are based on the information on fatal AEs. b. The following events are considered: symptomatic ARIA-E, symptomatic ARIA-H, serious ARIA-E and serious ARIA-H. c. Operationalized via the PT ‘Infusion-related reaction’; the SMQ ‘hypersensitivity’ is presented as supplementary information in the current data set. d. No suitable data available; see text below for explanation. e. The company did not present any data for the relevant subpopulations. f. No data are available on combined analyses of the events under consideration: symptomatic ARIA-E, symptomatic ARIA-H, serious ARIA-E and serious ARIA-H; furthermore, no data are available for symptomatic ARIA-H. g. No further specific AEs were identified based on the AEs occurring in the relevant study. AChEI: acetylcholinesterase inhibitor; ADAS-Cog13: Alzheimer’s Disease Assessment Scale-Cognitive subscale 13-item version; AE: adverse event; ARIA: amyloid-related imaging abnormalities; ARIA-E: amyloid related imaging abnormality-oedema/effusion; ARIA-H: amyloid related imaging abnormality-microhaemorrhages and haemosiderin deposits; CDR-SB: Clinical Dementia Rating-Sum of Boxes; QOL-AD: Quality of life in Alzheimer’s disease; RCT: randomized controlled trial; SAE: serious adverse event; SMQ: Standardized Medical Dictionary for Regulatory Activities Query; VAS: visual analogue scale												

Time-to-event analyses for permanent deterioration were used for the benefit assessment

In its dossier and in its comments on morbidity and quality of life outcomes, the company presented time-to-event analyses for permanent deterioration of 15% of the scale range in each case. The company did not present results with continuous analysis. Given the progressive nature of the disease, time-to-event analyses for permanent deterioration are preferable versus end-of-study analyses for outcomes relating to morbidity and quality of life.

Permanent deterioration was defined as a deterioration in the relevant response criterion without any subsequent improvement until the end of the study. A one-off deterioration – or, where applicable, a confirmed deterioration – following which only missing values occurred,

was also classified as a permanent deterioration. This approach was appropriate, as it also took into account any deterioration since the last study visit.

In its supplementary submission, the company provided additional information and sensitivity analyses, in particular regarding the observations at the end of the randomized study phase (Visit 21, corresponding to Week 76, with a visit window of ± 7 days). The company stated that all observations relating to the randomized phase (up to Visit 21) were included in the analysis. As some of the recordings took place outside the planned visit window (Day 533 + 7 days), in its supplementary submission the company provided additional sensitivity analyses taking into account only the recordings conducted within the window for Visit 21. The results of the sensitivity analyses are consistent with the main analyses (see Appendix F). Furthermore, the company presented data showing that a delayed Visit 21 – and thus an extended observation period – affected roughly the same number of patients in both the intervention arm and the comparator arm. In the population with CDR-GS 1 or 2, 14% of patients in the intervention arm and 17% of patients in the placebo arm had their visit (and thus the CDR-SB recording) take place outside the scheduled visit window, with a maximum of 601 days in the intervention arm and 596 days in the placebo arm [3]. In the population with CDR-SB values of 4.5 to 9.0, the data were comparable [3]. The data submitted subsequently allowed the time-to-event analyses to be used for the benefit assessment. Any remaining uncertainties arising from the high proportion of missing values at the end of the study were taken into account in the risk of bias for the relevant outcomes.

The time-to-event analyses relating to a permanent deterioration of 15% of the scale range in each case (including recordings conducted outside the planned visit window) were therefore used given the available data.

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 tool takes 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 6 domains: 3 cognitive domains (memory, orientation, judgement and problem-solving) and 3 functional domains (community affairs, home and hobbies, and personal care). The patient is only interviewed in relation to the 3 cognitive domains, whilst the carer is the sole person asked about the 3 functional domains. For each of the 6 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) [9,14].

Based on the 6 domain scores, 2 different overall scores can be calculated: CDR-GS and CDR-SB.

The CDR-GS distinguishes between 5 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) [9,14]. 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 5 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 [7,8].

The CDR-SB is calculated by adding the 6 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 6 domains contributes equally to the CDR-SB, and any change in 1 of the 6 domains has an immediate effect on the CDR-SB [7,15,16]. In comparison with the CDR-GS, the CDR-SB demonstrates greater sensitivity, particularly in the early stages of Alzheimer’s disease. For example, a patient with a CDR-GS score of 0.5 may have CDR-SB scores ranging from 0.5 to 5 [7,8,16,17].

CDR analyses in the form of CDR-SB are preferable to 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 were used for the benefit assessment.

The company submitted time-to-event analyses for the CDR-SB on permanent deterioration with the post hoc threshold of 2.7 points. Unlike the CDR-GS, the CDR-SB can be assumed to use interval scaling [7], meaning that responder analyses on changes by a proportion of the scale range can be interpreted. The threshold value of 2.7 points corresponds to exactly 15% of the scale range. As explained in the IQWiG *General Methods* [18], 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. A patient’s condition may therefore deteriorate by 2.5 or 3 points, but not by 2.7 points. It was therefore assumed that the company classified patients as responders once their condition had deteriorated by at least 3 points. The time-to-event analyses on permanent deterioration for the CDR-SB submitted by company concurred with the requirements of the methods paper and were used for the benefit assessment.

In its comments, the company also provided CDR-GS time-to-event analyses on permanent deterioration to a CDR-GS score of ≥ 2 , in order to represent the transition to the stage of

moderate dementia. Patients with a CDR-GS score of 2 at baseline were censored. However, it is unclear whether the CDR-GS can be used for the assessment of disease progression to the moderate stage because, as already described, the diagnosis is more complex and cannot currently be represented by a single tool. In this context, it would seem more sensible to revisit the physicians' diagnosis during the course of the study and assess the progression to a later stage of the disease in this way. Nevertheless, the time-to-event analysis on permanent deterioration to a CDR-GS ≥ 2 is presented here as supplementary information and may assist in interpreting the results relating to permanent deterioration in the CDR-SB.

Integrated Alzheimer's Disease Rating Scale (iADRS)

The iADRS was developed to assess treatment effects and disease progression in early-stage Alzheimer's disease (MCI or mild dementia) [19,20]. This is not a standalone instrument, but rather a composite scale comprising the ADAS-Cog13 and ADCS-iADL instruments described above [19,20]. Both instruments are fully incorporated into the iADRS, resulting in a scale range for the iADRS of 0 to 144 when the ADAS-Cog13 is used, with a lower score indicating a more severe impairment. Patients were not involved in the development of this tool.

As the iADRS takes into account both cognition and function, it represents the symptoms in the therapeutic indication in a similar way to the CDR. In this context, it should be noted that in the AACI study, the primary analysis was changed from CDR-SB to iADRS approximately 8 months after the start of the study. One reason given during the oral hearing was that the company had developed the instrument itself and preferred it for historical reasons [10]. However, what is more relevant for the benefit assessment is that, given the available data, the ADCS-iADL component was not considered to be sufficiently reliable for interpretation (see the section below). The CDR-SB provided analyses from an established and validated tool for assessing symptoms. Given the available data, the iADRS was therefore not used for the benefit assessment, but is presented for supplementary information (see Appendix E).

Cognition

ADAS-Cog13

The Alzheimer's Disease Assessment Scale-Cognitive subscale (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) [21,22]. Subsequent studies identified further items which are intended, amongst other things, to improve sensitivity to changes in the early stages of the disease [21,23]. In addition to the original 11 items, the ADAS-Cog13 also includes 2 of these additional items: Delayed Word Recall and Number Cancellation (crossing out specific digits from a series of numbers). The assessment 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 13 items in the ADAS-Cog13 is rated on a scale of 0 to 5 or 0 to 10 [24]. The scores for all items are added together to give a sum score, so that the ADAS-Cog13 scale ranges from 0 to 85, with a higher score indicating more severe cognitive impairment.

The company submitted analyses on deterioration by the post hoc threshold of 12.75 points for the ADAS-Cog13, which corresponds to exactly 15% of the scale. As explained in the IQWiG *General Methods* [18], 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 time-to-event analyses on permanent deterioration for the ADAS-Cog13 submitted by company concurred with the requirements of the methods paper and were used for the benefit assessment.

MMSE

The MMSE is a well-established tool for assessing cognition in Alzheimer's dementia. The MMSE was originally developed for patients with various neurological disorders, including different types of dementia [25,26]. The MMSE is recorded by the doctor. In the company study, the standard version of the MMSE with a scale range of 0–30 was used. Lower values indicate a greater degree of impairment.

The MMSE should be regarded as a validated tool for assessing cognition in Alzheimer's dementia [25]. The tool can be used for assessment in this therapeutic indication; however, where possible, the results of other tools should also be taken into account in the assessment. The ADAS-Cog13 provides a well established and more comprehensive tool for assessing cognition. The outcome cognition was therefore assessed on the basis of the ADAS-Cog13 analyses. The MMSE is therefore presented merely as supplementary information.

Independence in daily life and activities of daily living

Independence in daily life

As described in detail in the dossier assessment A25-111 [27], the outcome of independence in daily life is fundamentally relevant to patients and of particular importance in cases of dementia. Potential operationalizations of this outcome were also discussed in A25-111. For this benefit assessment, no suitable operationalization for assessing this outcome was available.

Activities of daily living (ADCS-iADL)

The Alzheimer's Disease Cooperative Study-instrumental Activities of Daily Living Inventory (ADCS-iADL) is a tool for recording impairment in instrumental activities of daily living in patients with Alzheimer's disease through third-party assessment [28]. It was derived from the original ADCS-ADL [29], which was developed to record impairment in activities of daily

living in patients with Alzheimer’s dementia. According to the company, the ADCS-ADL was recorded in full, but only those items relating to instrumental activities of daily living were analysed [28]. 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 [28,29].

The outcome activities of daily living, as a possible operationalization of independence in daily life, is relevant to patients. The ADCS-iADL can be used to record activities of daily living in patients with MCI or mild dementia due to Alzheimer’s disease; however, it can only be fully interpreted in conjunction with the complete questionnaire (ADCS-ADL) and the items not included (basic ADL). For this reason, the ADCS-iADL was not used for this benefit assessment. Furthermore, the ADCS-iADL is exclusively recorded through third-party assessment, even though 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-iADL is, in addition to patients with MCI, designed for patients with mild dementia caused by Alzheimer’s disease. Given the available data, the analyses were therefore not used for the benefit assessment. Regardless of this, there was no statistically significant difference between the study arms, either in the population with a CDR-GS of 1 or 2 or in the population with a CDR-SB of 4.5 to 9.0.

Behavioural changes

As the disease progresses, mental and behavioural symptoms develop in the 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, increasing impairment and the resulting social isolation [5,30]. Therefore, the outcome behavioural changes is, in principle, relevant to patients [30,31].

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 were 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 given therapeutic indication.

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 [32,33].

The validation study on the development of the QOL-AD did not distinguish between MCI and dementia. The study included individuals with mild cognitive impairment due to Alzheimer's disease (mean MMST score 22, range 18 to 28) [33]. It was 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 company submitted time-to-event analyses on permanent 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* [18], 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 Alzheimer's disease time-to-event analyses on permanent deterioration for the QOL-AD submitted by company concurred with the requirements of the methods paper and were used for the benefit assessment.

However, the company did not provide any analyses of the QOL-AD for the relevant subpopulations; consequently, no data were available for assessing health-related quality of life in research question 2.

Side effects

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 [34,35]. ARIA typically occur at an early stage of treatment and are usually asymptomatic [35]. 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 [34-36]. ARIA, as well as any associated symptoms, usually subside within weeks to months of treatment discontinuation [34,36]. If treatment is continued, ARIA may recur [36].

ARIA are categorized as ARIA-E and ARIA-H [34-36]. ARIA-E are characterized by parenchymal oedema, whilst ARIA-H are characterized by cerebral micro- and/or macrohaemorrhages,

superficial siderosis and sulcal or leptomeningeal haemosiderin deposits [34-36]. 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 [34]. In cases of mild, asymptomatic ARIA, treatment may be continued [4,34]. 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.

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 summary, symptomatic ARIA events are classified as relevant to the patient and were taken into account for this benefit assessment. The following events were considered: symptomatic ARIA-E and ARIA-H, as well as serious ARIA-E and ARIA-H. In addition, combined analyses of the events under consideration would also be required. However, for the relevant subpopulations no results were available for these combined analyses. There were also no data available for symptomatic ARIA-H.

Infusion-related reaction (AEs)

In the AACI study, infusion-related reactions were recorded as a Preferred Term (PT) as part of AE recording. 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.

Furthermore, the company considered hypersensitivity, using the Standardized MedDRA Query (SMQ), to be an AE of special interest. This considers events that may be related not only to an infusion, but also to hypersensitivity in general, and allergic reactions regardless of the infusion. Given the available data, it was assumed that the hypersensitivity outcome mainly comprised events from the PT infusion-related reactions (see also Table 8 and Table 10). Consequently, the PT infusion-related reactions provided a better representation of the relevant outcome and was used for the benefit assessment. The analysis using the SMQ hypersensitivity according to MedDRA is presented as supplementary information.

2.4.3.2 Risk of bias

Table 6 shows the risk of bias for the study AACI at outcome level.

Table 6: Risk of bias across outcomes and outcome-specific risk of bias – RCT, direct comparison: donanemab + AChEI vs. placebo + AChEI

Study	Study level	Outcomes											
		All-cause mortality ^a	Symptoms (CDR-SB)	Cognition (ADAS-Cog13)	Independence in daily life	Activities of daily living	Behavioural changes	Health-related quality of life (QOL-AD, patient-reported version)	SAEs	Discontinuation due to AEs	Symptomatic ARIA events ^b (AEs)	Infusion-related reactions ^c (PT, AEs)	Other specific AEs
AACI	L	L	H ^d	H ^d	– ^e	– ^e	– ^e	– ^f	L	L ^g	L ^h	L	–

a. The results on all-cause mortality are based on the information on fatal AEs.
 b. The following events are considered: symptomatic ARIA-E, symptomatic ARIA-H, serious ARIA-E and serious ARIA-H.
 c. Operationalized via the PT ‘Infusion-related reaction’; the SMQ ‘hypersensitivity’ is presented as supplementary information in the current data set.
 d. Large proportion of incomplete observations for potentially informative reasons.
 e. No suitable data available.
 f. The company did not present any data for the relevant subpopulations.
 g. Despite the low risk of bias, the certainty of results is presumably limited for the outcome discontinuation due to AEs.
 h. No data are available for symptomatic ARIA-H; furthermore, no data are available for the patients with event for symptomatic ARIA-E, symptomatic ARIA-H, serious ARIA-E or serious ARIA-H as a composite outcome.

AChEI: acetylcholinesterase inhibitor; ADAS-Cog13: Alzheimer’s Disease Assessment Scale-Cognitive subscale 13-item version; AE: adverse event; ARIA: amyloid related imaging abnormalities; ARIA-E: amyloid related imaging abnormality-oedema/effusion; ARIA-H: amyloid related imaging abnormality-microhaemorrhages and haemosiderin deposits; CDR-SB: Clinical Dementia Rating-Sum of Boxes; H: high; L: low; PT: Preferred Term; QOL-AD: Quality of life in Alzheimer’s disease; RCT: randomized controlled trial; SMQ: Standardized Medical Dictionary for Regulatory Activities Query; SAE: serious adverse event

The risk of bias in the results for the outcomes of all-cause mortality, SAEs, symptomatic ARIA events and infusion-related reactions was assessed as low.

With regard to the results for the outcomes symptoms and cognition, the risk of bias was assessed as high due to the high proportion of incomplete observations for potentially informative reasons due to study discontinuations. For the health-related quality of life outcome, the company did not provide any data in its comments for the subpopulations under consideration; consequently, the risk of bias was not assessed.

Although the risk of bias for the outcome discontinuation due to AEs was low, the certainty of results for this outcome was limited. Premature treatment discontinuation for reasons other than AEs is a competing event for the outcome discontinuation due to AEs to be recorded. 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.

Consideration of further aspects of the certainty of conclusions

Dossier assessment A25-134 described limitations which the company only partially addressed with the subsequently submitted data (see Section 2.1). In particular, the lack of information on dosage and adjustment of AChEI therapy, the lack of information on handling lack of effectiveness or progression to the next stage, and the lack of information on non-drug therapies all led to a reduced certainty of conclusions. In addition, there was a degree of uncertainty in the populations under consideration due to the small proportion of patients in each group who were administered a 700 mg dose of donanemab that did not comply with the SmPC, patients who may have still been at the MCI stage or already at the stage of moderate dementia at baseline, and patients with contraindications. Each of these groups was, on its own, considered too small to cause any relevant bias. However, it was unclear to what extent these groups comprised the same or distinct patients, and what the overall proportion of patients with potentially confounding characteristics was.

Summary assessment of the certainty of conclusions

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

2.4.3.3 Results

Table 7, Table 8, Table 9 and Table 10 summarize the results on the comparison of donanemab + AChEI vs. placebo + AChEI for the subpopulations under consideration. Where necessary, calculations conducted by the Institute are provided in addition to the data from the company's comments.

The Kaplan-Meier curves on the time-to-event analyses are presented in Appendix F and the tables on common AEs, common SAEs, and discontinuations due to AEs can be found in Appendix G.

Table 7: Results (morbidity, health-related quality of life) – RCT, direct comparison: donanemab + AChEI vs. placebo + AChEI (subpopulation with CDR-GS 1 or 2)

Study	donanemab + AChEI		placebo + AChEI		donanemab + AChEI vs. placebo + AChEI
Outcome category					
Outcome	N	Median time to event (weeks) [95% CI] Patients with event n (%)	N	Median time to event (weeks) [95% CI] Patients with event n (%)	HR [95% CI]; p-value ^a
AACI					
Morbidity					
Symptoms (CDR-SB – time to permanent deterioration ^{b, c})	122	77.3 [77.00; NC] 36 (29.5)	110	77.0 [75.71; NC] 45 (40.9)	0.80 [0.51; 1.25]; 0.320
<i>Symptoms (time to permanent deterioration on the CDR-GS ≥ 2^b, supplementary presentation)</i>	122	82.9 [76.29; NC] 34 (27.9)	110	79.0 [77.00; NC] 35 (31.8)	1.03 [0.64; 1.66]; 0.910
Cognition (ADAS-Cog13 – time to permanent deterioration ^{b, d})	122	NA [78.14; NC] 20 (16.4)	110	79.9 [76.71; NC] 33 (30.0)	0.60 [0.34; 1.06]; 0.079
<i>MMSE^{b, e} (supplementary presentation)</i>	122	76.9 [76.57; NC] 36 (29.5)	110	77.4 [75.86; 79.43] 43 (39.1)	0.89 [0.57; 1.39]; 0.609
No suitable data available for independence in daily life, activities of daily living and behavioural changes					
Health-related quality of life					
QOL-AD – time to permanent deterioration ^{b, f}	No data presented				
a. Stratified Cox proportional hazards model with treatment, age, baseline value and use of AChEI at baseline as fixed effects, and the tau category at baseline as a stratification factor.					
b. A permanent deterioration was defined as the first point in time at which the relevant response criterion was met without any subsequent improvement until the end of the study, or when, following an initial (or, where applicable, confirmed) deterioration, only missing values occurred.					
c. An increase of the score by ≥ 2.7 points (15% of the scale range) from baseline is considered a clinically relevant deterioration (score range of the scale: 0 to 18).					
d. An increase of ≥ 12.75 points (15% of the scale range) from baseline is considered a clinically relevant deterioration (score range of the scale: 0 to 85).					
e. A decrease of ≥ 4.50 points (15% of the scale range) from baseline is considered a clinically relevant deterioration (score range of the scale: 0 to 30).					
f. A decrease of ≥ 5.85 points (15% of the scale range) from baseline is considered a clinically relevant deterioration (score range of the scale: 13 to 52).					
AChEI: acetylcholinesterase inhibitor; ADAS-Cog13: Alzheimer’s Disease Assessment Scale-Cognitive subscale 13-item version; CDR-GS: Clinical Dementia Rating-Global Score; CDR-SB: Clinical Dementia Rating-Sum of Boxes; CI: confidence interval; HR: hazard ratio; MMSE: Mini-Mental State Examination; N: number of analysed patients; n: number of patients with event; NA: not achieved; NC: not calculable; QOL-AD: Quality of life in Alzheimer’s disease; RCT: randomized controlled trial					

Table 8: Results (mortality, side effects) – RCT, direct comparison: donanemab + AChEI vs. placebo + AChEI (subpopulation with CDR-GS 1 or 2)

Study Outcome category Outcome	donanemab + AChEI		placebo + AChEI		donanemab + AChEI vs. placebo + AChEI
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p-value ^a
AACI					
Mortality					
All-cause mortality ^b	120	6 (5.0)	110	1 (0.9)	5.50 [0.67; 44.96]; 0.122
Side effects					
AEs (supplementary information)	120	107 (89.2)	110	90 (81.8)	
SAEs	120	27 (22.5)	110	17 (15.5)	1.46 [0.84; 2.52]; 0.184
Discontinuation due to AEs	120	20 (16.7)	110	6 (5.5)	3.06 [1.27; 7.33]; 0.011
Symptomatic ARIA events					
Symptomatic ARIA events ^c			No data presented		
Symptomatic ARIA-E	120	4 (3.3)		0 (0)	8.26 [0.45; > 100]; 0.123
Symptomatic ARIA-H				ND	
Serious ARIA-E	120	0 (0)	110	0 (0)	–
Serious ARIA-H	120	1 (0.8)	110	0 (0)	2.75 [0.11; 66.86]; > 0.999
Infusion-related reactions ^d (PT, AEs)	120	7 (5.8)	110	0 (0)	13.76 [0.80; > 100]; 0.015
<i>Hypersensitivity (SMQ narrow, AEs; supplementary presentation)</i>	120	12 (10.0)	110	3 (2.7)	3.67 [1.06; 12.65]; 0.032
a. Unstratified Mantel-Haenszel approach, 95% CI based on Wald, p-value based on Fisher exact test. b. The results on all-cause mortality are based on the data on fatal AEs. c. Combined analyses on the following events are considered: symptomatic ARIA-E, symptomatic ARIA-H, serious ARIA-E and serious ARIA-H. d. Operationalized via the PT ‘infusion-related reaction’; the SMQ ‘hypersensitivity’ is presented as supplementary information in the current data set (see also Section 2.4.3.1). AChEI: acetylcholinesterase inhibitor; AE: adverse event; ARIA: amyloid related imaging abnormalities; ARIA-E: amyloid related imaging abnormality-oedema/effusion; ARIA-H: amyloid related imaging abnormality-microhaemorrhages and hemosiderin deposits; CDR-GS: Clinical Dementia Rating-Global Score; CI: confidence interval; n: number of patients with (at least one) event; N: number of patients who received at least one dose of the study medication; ND: no data; MedDRA: Medical Dictionary for Regulatory Activities; PT: Preferred Term; RR: relative risk; SAE: serious adverse event; SMQ: Standardized MedDRA Query					

Table 9: Results (morbidity, health-related quality of life) – RCT, direct comparison: donanemab + AChEI vs. placebo + AChEI (subpopulation with CDR-SB 4.5 to 9)

Study Outcome category Outcome	donanemab + AChEI		placebo + AChEI		donanemab + AChEI vs. placebo + AChEI
	N	Median time to event (weeks) [95% CI] Patients with event n (%)	N	Median time to event (weeks) [95% CI] Patients with event n (%)	HR [95% CI]; p-value ^a
AACI					
Morbidity					
Symptoms (CDR-SB – time to permanent deterioration ^{b, c})	119	79.0 [77.00; NC] 33 (27.7)	107	77.0 [75.71; NC] 42 (39.3)	0.75 [0.47; 1.19]; 0.218
Symptoms (<i>time to permanent deterioration on the CDR-GS ≥ 2^b, supplementary presentation</i>)	119	82.9 [76.57; NC] 32 (26.9)	107	79.0 [76.71; NC] 33 (30.8)	0.93 [0.57; 1.52]; 0.764
Cognition (ADAS-Cog13 – time to permanent deterioration ^{b, d})	119	NA [78.14; NC] 19 (16.0)	107	NA [76.71; NC] 30 (28.0)	0.56 [0.31; 0.9997]; 0.0499
MMSE ^{b, e} (<i>supplementary presentation</i>)	119	77.0 [76.57; NC] 32 (26.9)	107	77.1 [75.86; 79.43] 42 (39.3)	0.79 [0.50; 1.26]; 0.323
No suitable data available for independence in daily life, activities of daily living and behavioural changes					
Health-related quality of life					
QOL-AD – time to permanent deterioration ^{b, f}	No data presented				
a. Stratified Cox proportional hazards model with treatment, age, baseline value and use of AChEI at baseline as fixed effects, and the tau category at baseline as a stratification factor. b. A permanent deterioration was defined as the first point in time at which the relevant response criterion was met without any subsequent improvement until the end of the study, or when, following an initial (or, where applicable, confirmed) deterioration, only missing values occurred. c. An increase of the score by ≥ 2.7 points (15% of the scale range) from baseline is considered a clinically relevant deterioration (score range of the scale: 0 to 18). d. An increase of ≥ 12.75 points (15% of the scale range) from baseline is considered a clinically relevant deterioration (score range of the scale: 0 to 85). e. A decrease of ≥ 4.50 points (15% of the scale range) from baseline is considered a clinically relevant deterioration (score range of the scale: 0 to 30). f. A decrease of ≥ 5.85 points (15% of the scale range) from baseline is considered a clinically relevant deterioration (score range of the scale: 13 to 52).					
AChEI: acetylcholinesterase inhibitor; ADAS-Cog13: Alzheimer’s Disease Assessment Scale-Cognitive subscale 13-item version; CDR-GS: Clinical Dementia Rating-Global Score; CDR-SB: Clinical Dementia Rating-Sum of Boxes; CI: confidence interval; HR: hazard ratio; MMSE: Mini-Mental State Examination; N: number of analysed patients; n: number of patients with event; NA: not achieved; NC: not calculable; QOL-AD: Quality of life in Alzheimer’s disease; RCT: randomized controlled trial					

Table 10: Results (mortality, side effects) – RCT, direct comparison: donanemab + AChEI vs. placebo + AChEI (subpopulation with CDR-SB 4.5 to 9)

Study Outcome category Outcome	donanemab + AChEI		placebo + AChEI		donanemab + AChEI vs. placebo + AChEI
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p-value ^a
AACI					
Mortality					
All-cause mortality ^b	117	6 (5.1)	107	1 (0.9)	5.49 [0.67; 44.84]; 0.122
Side effects					
AEs (supplementary information)	117	105 (89.7)	107	84 (78.5)	–
SAEs	117	25 (21.4)	107	16 (15.0)	1.43 [0.81; 2.53]; 0.231
Discontinuation due to AEs	117	19 (16.2)	107	5 (4.7)	3.48 [1.34; 8.98]; 0.008
Symptomatic ARIA events					
Symptomatic ARIA events ^c			No data presented		
Symptomatic ARIA-E	117	5 (4.3)	107	0 (0.0)	10.07 [0.56; > 100]; 0.061
Symptomatic ARIA-H				ND	
Serious ARIA-E	117	1 (0.9)	107	0 (0.0)	2.75 [0.11; 66.69]; > 0.999
Serious ARIA-H	117	1 (0.9)	107	0 (0.0)	2.75 [0.11; 66.69]; > 0.999
Infusion-related reactions ^d (PT, AEs)	117	8 (6.8)	107	0 (0.0)	15.56 [0.91; > 100]; 0.007
<i>Hypersensitivity (SMQ narrow, AEs; supplementary presentation)</i>	117	12 (10.3)	107	4 (3.7)	2.74 [0.91; 8.25]; 0.071
a. Unstratified Mantel-Haenszel approach, 95% CI based on Wald, p-value based on Fisher exact test. b. The results on all-cause mortality are based on the data on fatal AEs. c. Combined analyses on the following events are considered: symptomatic ARIA-E, symptomatic ARIA-H, serious ARIA-E and serious ARIA-H. d. Operationalized via the PT ‘infusion-related reaction’; the SMQ ‘hypersensitivity’ is presented as supplementary information in the current data set (see also Section 2.4.3.1). AChEI: acetylcholinesterase inhibitor; AE: adverse event; ARIA: amyloid related imaging abnormalities; ARIA-E: amyloid related imaging abnormality-oedema/effusion; ARIA-H: amyloid-related imaging abnormality-microhaemorrhages and hemosiderin deposits; CDR-SB: Clinical Dementia Rating-Sum of Boxes; CI: confidence interval; n: number of patients with (at least one) event; MedDRA: Medical Dictionary for Regulatory Activities; N: number of patients who received at least one dose of the study medication; ND: no data; PT: Preferred Term; RR: relative risk; SAE: serious adverse event; SMQ: Standardized MedDRA Query					

Based on the available information, at most hints, e.g. of an added benefit, can be determined for all data subsequently submitted with the comments (see Section 2.4.3.2 of this addendum for reasoning).

Mortality

There was no statistically significant difference between the treatment arms in either subpopulation for the outcome all-cause mortality. There is no hint of an added benefit of donanemab + AChEI in comparison with AChEI; an added benefit is therefore not proven.

Morbidity

Symptoms (CDR-SB)

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

Cognition (ADAS-Cog13)

For the outcome cognition, recorded using ADAS-Cog13, there was no statistically significant difference between the treatment arms in the subpopulation formed according to CDR-GS. For the subpopulation formed according to CDR-SB, however, there was a statistically significant difference in favour of donanemab + AChEI compared with AChEI.

A comparison with the population prior to CDR filtering (HR: 0.63 [0.40; 0.98] [2]) showed that the patients with mild Alzheimer's dementia and a CDR-GS of 0.5 or a CDR-SB of less than 4.5 – who were no longer included in the analysis and who may have constituted a large proportion of patients included in research question 2 – would potentially shift the HR effect estimate in the ADAS-Cog13 (HR: 0.56 [0.31; 0.9997] [2]) in a direction to the disadvantage of the intervention. Furthermore, despite the subpopulations of the company overlapping almost completely, the effect in the ADAS-Cog13 was statistically significant when filtered by AChEI treatment and CDR-SB, but was not statistically significant when filtered by AChEI treatment and CDR-GS, and was therefore assessed as non-robust. Considering both populations together, there is no hint of an added benefit of donanemab + AChEI compared with AChEI; an added benefit is therefore not proven.

Independence in daily life , activities of daily living, behavioural changes

No suitable data were available for the outcomes of independence in daily life, activities of daily living and behavioural changes for either subpopulation (see Section 2.4.3.1 for reasons). There is no hint of an added benefit of donanemab + AChEI in comparison with AChEI; an added benefit is therefore not proven.

Health-related quality of life (QOL-AD)

No data were available for the health-related quality of life outcome, assessed using the QOL-AD, for the subpopulations considered here. There is no hint of greater or lesser harm of donanemab + AChEI in comparison with AChEI; an added benefit is therefore not proven.

Side effects

SAEs

There was no statistically significant difference between the treatment arms in either subpopulation for the outcome SAEs. There is no hint of greater or lesser harm of donanemab + AChEI in comparison with AChEI; greater or lesser harm is therefore not proven.

Discontinuation due to AEs

For the outcome discontinuation due to AEs, there was a statistically significant difference to the disadvantage of donanemab + AChEI in comparison AChEI. There was a hint of greater harm of donanemab + AChEI in comparison with AChEI.

Symptomatic ARIA events

With regard to the outcome symptomatic ARIA events, there was no statistically significant difference between the treatment groups in either subpopulation when symptomatic ARIA-E, serious ARIA-E and serious ARIA-H were considered. No data were available for symptomatic ARIA-H or for combined analyses. There is no hint of greater or lesser harm of donanemab + AChEI in comparison with AChEI in either case; greater or lesser harm is therefore not proven.

Infusion-related reactions (PT, AE)

A statistically significant difference to the disadvantage of donanemab + AChEI compared with AChEI was shown for the outcome infusion-related reactions. There was a discrepancy between the confidence interval and the p-value. The difference was therefore no more than marginal for this outcome in the category non-serious/non-severe side effects in the subpopulation under consideration (see also Section 2.4.4.1). There is no hint of greater or lesser harm of donanemab + AChEI in comparison with AChEI; greater or lesser harm is therefore not proven.

2.4.3.4 Subgroups and other effect modifiers

The following potential effect modifiers were considered for this 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. There were no suitable subgroup characteristics available to categorize the severity of the condition within a population of patients with mild Alzheimer's dementia. Within the study, subgroup analyses based on the MMSE with the groups 27 to 30 and 20 to 26 were planned. Within the subpopulations considered here, it was assumed that only a few patients had an MMSE score of at least 27.

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 ($p\text{-value} < 0.05$) are presented. In addition, subgroup results are only presented if there is a statistically significant and relevant effect in at least one subgroup.

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

2.4.4 Probability and extent of added benefit

The probability and extent of added benefit at outcome level are derived below, taking into account the different outcome categories and effect sizes. The methods used for this purpose are explained in the *General Methods* of IQWiG [18].

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

2.4.4.1 Assessment of added benefit at outcome level

The extent of the respective added benefit at outcome level was assessed based on the results presented in Section 2.4.3.3 (see Table 11).

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

Table 11: Extent of added benefit at outcome level: donanemab + AChEI vs. AChEI (research question 2) (multipage table)

Outcome category Outcome Subpopulation	donanemab + AChEI vs. AChEI Proportion of events (%) or median time to event (weeks) Effect estimation [95% CI]; p-value Probability ^a	Derivation of extent ^b
Mortality		
All-cause mortality		
CDR-GS 1 or 2	5.0% vs. 0.9% RR: 5.50 [0.67; 44.96]; p = 0.122	Lesser benefit not proven / added benefit not proven
CDR-SB 4.5 to 9	5.1% vs. 0.9% RR: 5.49 [0.67; 44.84]; p = 0.122	
Morbidity		
Symptoms (CDR-SB – time to permanent deterioration)		
CDR-GS 1 or 2	77.3 vs. 77.0 weeks HR: 0.80 [0.51; 1.25]; p = 0.320	Lesser benefit not proven / added benefit not proven
CDR-SB 4.5 to 9	79.0 vs. 77.0 HR: 0.75 [0.47; 1.19]; p = 0.218	
Cognition (ADAS-Cog13 – time to permanent deterioration)		
CDR-GS 1 or 2	NA vs. 79.9 weeks HR: 0.60 [0.34; 1.06]; p = 0.079	Lesser benefit not proven / added benefit not proven ^c
CDR-SB 4.5 to 9	NA vs. NA HR: 0.56 [0.31; 0.9997]; p = 0.0499	
Independence in daily life	No suitable data	Lesser benefit not proven / added benefit not proven
Activities of daily living	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-related quality of life		
QOL-AD – time to permanent deterioration	ND vs. ND RR: –; p: –	Lesser benefit not proven / added benefit not proven

Table 11: Extent of added benefit at outcome level: donanemab + AChEI vs. AChEI (research question 2) (multipage table)

Outcome category Outcome Subpopulation	donanemab + AChEI vs. AChEI Proportion of events (%) or median time to event (weeks) Effect estimation [95% CI]; p-value Probability ^a	Derivation of extent ^b
Side effects		
SAEs		
CDR-GS 1 or 2	22.5% vs. 15.5% RR: 1.46 [0.84; 2.52]; p = 0.184	Greater/lesser harm not proven
CDR-SB 4.5 to 9	21.4% vs. 15.0% RR: 1.43 [0.81; 2.53]; p = 0.231	
Discontinuation due to AEs		
CDR-GS 1 or 2	16.7% vs. 5.5% RR: 3.06 [1.27; 7.33] RR: 0.33 [0.14; 0.79] ^d ; p = 0.011 Probability: hint	Outcome category: non-serious/non-severe side effects CI _u < 0.80 greater harm, extent: considerable
CDR-SB 4.5 to 9	16.2% vs. 4.7% RR: 3.48 [1.34; 8.98] RR: 0.29 [0.11; 0.75] ^d ; p = 0.008 Probability: hint	
Symptomatic ARIA events		
Symptomatic ARIA events	ND vs. ND RR: —; p: —	Greater/lesser harm not proven
Symptomatic ARIA-E		
CDR-GS 1 or 2	3.3% vs. 0% RR: 8.26 [0.45; > 100]; p = 0.123	Greater/lesser harm not proven
CDR-SB 4.5 to 9	4.3% vs. 0% RR: 10.07 [0.56; > 100]; p = 0.061	
Symptomatic ARIA-H	ND vs. ND RR: —; p: —	Greater/lesser harm not proven

Table 11: Extent of added benefit at outcome level: donanemab + AChEI vs. AChEI (research question 2) (multipage table)

Outcome category Outcome Subpopulation	donanemab + AChEI vs. AChEI Proportion of events (%) or median time to event (weeks) Effect estimation [95% CI]; p-value Probability ^a	Derivation of extent ^b
Serious ARIA-E CDR-GS 1 or 2	0% vs. 0% RR: –; p: –	Greater/lesser harm not proven
CDR-SB 4.5 to 9	0.9% vs. 0% RR: 2.75 [0.11; 66.69]; p > 0.999	
Serious ARIA-H CDR-GS 1 or 2	0.8% vs. 0% RR: 2.75 [0.11; 66.86]; p > 0.999	Greater/lesser harm not proven
CDR-SB 4.5 to 9	0.9% vs. 0% RR: 2.75 [0.11; 66.69]; p > 0.999	
Infusion-related reactions (PT, AEs)		
CDR-GS 1 or 2	5.8% vs. 0% RR: 13.76 [0.80; > 100]; RR: 0.07 [< 0.01; 1.25] ^d ; p = 0.015 Probability: hint	Outcome category: non-serious/non-severe symptoms/late complications 1 < CI _u ; p < 0.05 Lesser benefit not proven/added benefit not proven ^e
CDR-SB 4.5 to 9	6.8% vs. 0% RR: 15.56 [0.91; > 100] RR: 0.06 [< 0.01; 1.10] ^d ; p = 0.007 Probability: hint	
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. Given the available data, the effects are not suitable for the derivation of an added benefit (see also Section 2.4.3.3). d. Institute’s calculation; reversed direction of effect to enable the use of limits to derive the extent of added benefit. e. Discrepancy between CI and p-value. The result of the statistical test (p-value) is decisive for the derivation of the added benefit. The extent of the effect in this non-serious/non-severe outcome was no more than marginal.		

Table 11: Extent of added benefit at outcome level: donanemab + AChEI vs. AChEI (research question 2) (multipage table)

Outcome category Outcome Subpopulation	donanemab + AChEI vs. AChEI Proportion of events (%) or median time to event (weeks) Effect estimation [95% CI]; p-value Probability ^a	Derivation of extent ^b
AChEI: acetylcholinesterase inhibitor; ADAS-Cog13: Alzheimer's Disease Assessment Scale-Cognitive subscale 13-item version; AE: adverse event; ARIA: amyloid related imaging abnormalities; ARIA-E: amyloid related imaging abnormality-oedema/effusion; ARIA-H: amyloid related imaging abnormality-microhaemorrhages and haemosiderin deposits; CDR-GS: Clinical Dementia Rating-Global Score; CDR-SB: Clinical Dementia Rating-Sum of Boxes; CI: confidence interval; CI _u : upper limit of confidence interval; HR: hazard ratio; NA: not achieved; ND: no data; PT: Preferred Term; QOL-AD: Quality of life in Alzheimer's disease; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event		

2.4.4.2 Overall conclusion on added benefit

Table 12 summarizes the results taken into account for the overall conclusion on the extent of the added benefit.

Table 12: Positive and negative effects from the assessment of donanemab + AChEI in comparison with AChEI

Positive effects	Negative effects
–	Non-serious/non-severe side effects Discontinuation due to AEs: hint of greater harm – extent: considerable
No suitable data were available for the outcomes of independence in daily life, activities of daily living, behavioural changes, health-related quality of life measured using the QOL-AD, symptomatic ARIA-H, or combined ARIA events.	
AChEI: acetylcholinesterase inhibitor; AE: adverse event; ARIA: amyloid related imaging abnormalities; ARIA-H: amyloid related imaging abnormality-microhaemorrhage and haemosiderin deposits; QOL-AD: Quality of Life in Alzheimer's Disease	

Taking into account the analyses submitted subsequently during the commenting procedure, a negative effect was shown for research question 2 in the category of non-serious/non-severe side effects for the outcome discontinuation due to AEs, with considerable extent.

For the outcome infusion-related reactions, the confidence interval covers the zero effect. No data were available on health-related quality of life measured using QOL-AD, symptomatic ARIA-H or combined ARIA events. The study did not record the outcomes independence in daily life, activities of daily living or behavioural changes.

In the overall analysis of the available results, the negative effect in the outcome discontinuation due to AEs was not considered sufficient for the derivation of a lesser benefit of donanemab. Furthermore, it was assumed that the missing analyses would not contain any negative effects of such a magnitude that they would ultimately result in a lesser benefit overall.

Summary

In summary, the available data provide no hint of an added benefit of donanemab (as add-on therapy to ongoing AChEI treatment) 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.

2.5 Summary

The data subsequently submitted by the company in the commenting procedure did not alter the conclusion on the added benefit of donanemab drawn in dossier assessment A25-134.

The following Table 13 shows the result of the benefit assessment of donanemab, taking into account dossier assessment A25-134 and this addendum.

Table 13: Donanemab – probability and extent of added benefit

Research question	Therapeutic indication	ACT ^a	Probability and extent of added benefit
Adults with early Alzheimer's disease with confirmed amyloid pathology who are ApoE ε4 non-carriers or heterozygotes:			
1	with clinically diagnosed MCI due to Alzheimer's disease	watchful waiting ^b	Added benefit not proven
2	with clinically diagnosed mild dementia due to Alzheimer's disease	donepezil or galantamine or rivastigmine ^{b, c}	Added benefit not proven ^d
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. The AChEIs (donepezil, galantamine and rivastigmine) are approved for the symptomatic treatment of mild to moderate Alzheimer's dementia. The aim should be to administer the highest tolerable dose. For the benefit assessment, the on-label use of drugs within the context of a study must be observed. d. Only patients with a CDR-GS of 1 or 2, or a CDR-SB of between 4.5 and 9, were included in the relevant subpopulations. It remained unclear whether the observed results can be transferred to patients with mild Alzheimer's dementia and different CDR scores. AChEI: acetylcholinesterase inhibitor; ApoE ε4: apolipoprotein E ε4; CDR-GS: Clinical Dementia Rating-Global Score; CDR-SB: Clinical Dementia Rating-Sum of Boxes; G-BA: Federal Joint Committee; MCI: mild cognitive impairment			

The G-BA decides on the added benefit.

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Appendix A Comparison of disease-related patient characteristics for the subsequently submitted subpopulations

Table 14: Comparison of disease-related patient characteristics for the subsequently submitted subpopulations without AChEI treatment

Study Characteristic Category	Subpopulation without AChEI + MMSE 27 to 30		Subpopulation without AChEI + CDR-GS 0.5		Subpopulation without AChEI + CDR-SB 0.5 to 4.0	
	donanemab N ^a = 77	placebo N ^a = 53	donanemab N ^a = 205	placebo N ^a = 187	donanemab N ^a = 202	placebo N ^a = 186
AACI						
Time since symptom onset [years], mean (SD)	3.57 (2.89)	3.55 (2.35)	3.42 (2.82)	3.37 (2.31)	3.43 (2.81)	3.37 (2.31)
Time since diagnosis of Alzheimer's disease [years], mean (SD)	0.90 (1.46)	0.94 (1.96)	0.75 (1.17)	0.86 (1.57)	0.73 (1.15)	0.84 (1.55)
MMSE, mean (SD)	— ^b	— ^b	24.64 (3.38)	24.09 (3.29)	24.62 (3.33)	24.07 (3.28)
MMSE score, n (%)						
27-30	77 (100)	53 (100)	ND	ND	ND	ND
20-26	0 (0)	0 (0)	ND	ND	ND	ND
CDR-SB, mean (SD)	2.11 (1.39)	2.09 (1.26)	2.40 (1.05)	2.45 (1.04)	2.36 (1.00)	2.43 (1.02)
CDR-GS, n (%)						
0	1 (1)	2 (4)	0 (0)	0 (0)	0 (0)	0 (0)
0.5	72 (94)	48 (91)	205 (100)	187 (100)	200 (99)	185 (100)
1	4 (5)	3 (6)	0 (0)	0 (0)	2 (1)	1 (< 1)
2	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
ADAS-Cog13, mean (SD)	19.69 (6.47)	19.15 (6.34)	23.52 (8.01)	24.19 (7.48)	23.40 (7.87)	24.05 (7.35)
a. Number of randomized patients; values that are based on other patient numbers are marked in the corresponding line if the deviation is relevant. b. According to information from the company, the means are below 27. This does not seem plausible. AChEI: acetylcholinesterase inhibitor; ADAS-Cog13: Alzheimer's Disease Assessment Scale-Cognitive subscale 13-item version; CDR-GS: Clinical Dementia Rating-Global Score; CDR-SB: Clinical Dementia Rating-Sum of Boxes; MMSE: Mini Mental State Examination; n: number of patients in the category; N: number of randomized patients; ND: no data; SD: standard deviation						

Table 15: Comparison of disease-related patient characteristics for the subsequently submitted subpopulations with AChEI treatment

Study Characteristic Category	Subpopulation with AChEI + MMSE 20 to 26		Subpopulation with AChEI + CDR-GS 1 or 2		Subpopulation with AChEI + CDR-SB 4.5 to 9	
	donanemab N ^a = 249	placebo N ^a = 246	donanemab N ^a = 122	placebo N ^a = 110	donanemab + AChEI N ^a = 119	placebo + AChEI N ^a = 107
AACI						
Time since symptom onset [years], mean (SD)	4.00 (2.32)	3.69 (1.99)	4.39 (2.33)	3.81 (1.97)	4.41 (2.31)	3.93 (2.05)
Time since diagnosis of Alzheimer's disease [years], mean (SD)	1.50 (1.56)	1.29 (1.45)	1.74 (1.78)	1.48 (1.71)	1.80 (1.75)	1.51 (1.62)
MMSE, mean (SD)	21.51 (3.52)	21.27 (3.40)	20.09 (3.43)	20.35 (3.47)	20.26 (3.41)	20.29 (3.38)
MMSE score, n (%)						
27-30	0 (0)	0 (0)	ND	ND	ND	ND
20-26	249 (100)	246 (100)	ND	ND	ND	ND
CDR-SB, mean (SD)	4.36 (2.01)	4.11 (1.69)	5.95 (1.52)	5.71 (1.45)	5.72 (1.14)	5.68 (1.26)
CDR-GS, n (%)						
0	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
0.5	129 (52)	146 (59)	0 (0)	0 (0)	6 (5)	6 (6)
1	106 (43)	97 (39)	112 (92)	106 (96)	109 (92)	99 (93)
2	10 (4)	3 (1)	10 (8)	4 (4)	4 (3)	2 (2)
ADAS-Cog13, mean (SD)	30.85 (8.23)	30.81 (8.46)	34.31 (8.26)	33.61 (8.05)	33.53 (7.93)	33.39 (8.08)
a. Number of randomized patients; values that are based on other patient numbers are marked in the corresponding line if the deviation is relevant. AChEI: acetylcholinesterase inhibitor; ADAS-Cog13: Alzheimer's Disease Assessment Scale-Cognitive subscale 13-item version; CDR-GS: Clinical Dementia Rating-Global Score; CDR-SB: Clinical Dementia Rating-Sum of Boxes; MMSE: Mini Mental State Examination; n: number of patients in the category; N: number of randomized patients; ND: no data; SD: standard deviation						

Appendix B Informative figures on the CDR-SB and its domains

Degree of impairment and score		None 0	Questionable 0.5	Mild 1	Moderate 2	Severe 3
Cognition	Memory	No memory loss or slight inconstant forgetfulness	Consistent slight forgetfulness; partial recoll. of events; 'benign' forgetfulness	Moderate memory loss; more marked for recent events; defect interferes with everyday activities	Severe memory loss; only highly learned material retained; new material rapidly lost	Severe memory loss; only fragments remain
	Orientation	Fully oriented	Fully oriented except for slight difficulty with time relationships	Moderate difficulty with time relationships; oriented for place at examination; may have geographical disorientation elsewhere	Severe difficulty with time relationships; usually disoriented to time, often to place	Orientation to person only
	Judgement and problem-solving	Solves everyday problems and handles business and financial affairs well; judgement good in relation to past performance	Slight impairment in solving problems, similarities and differences	Moderate difficulty in handling problems, similarities, and differences; social judgment usually maintained	Severely impaired in handling problems, similarities, and differences; social judgement usually impaired	Unable to make judgements or solve problems
Functioning	Community affairs	Independent function at usual level in job, shopping, and volunteer and social groups	Slight impairment in these activities	Unable to function independently at these activities although may still be engaged in some; appears normal to casual inspection	No pretence of independent function outside the home	
					Appears well enough to be taken to functions outside a family home	Appears too ill to be taken to functions outside a family home
	Home and hobbies	Life at home, hobbies, and intellectual interests well maintained	Life at home, hobbies, and intellectual interests slightly impaired	Mild but definite impairment of function at home; more difficult chores abandoned; more complicated hobbies and interests abandoned	Only simple chores preserved; very restricted interests, poorly maintained	No significant function in home
	Personal care	Fully capable of self-care		Needs prompting	Requires assistance in dressing, hygiene, keeping of personal effects	Requires much help with personal care; frequent incontinence

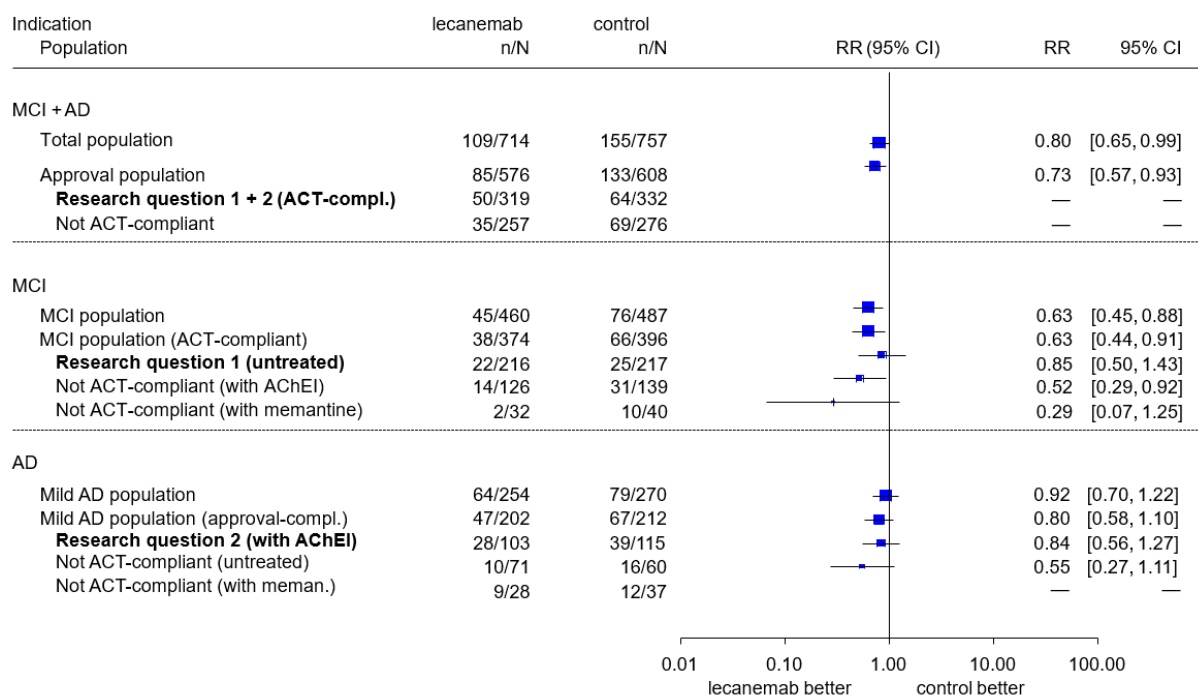
Figure 3: Domains of the CDR-SB, including degree of impairment and scores

CDR-GS		0	0.5 X	1	2	3
Degree of impairment and score		None 0	Questionable 0.5	Mild 1	Moderate 2	Severe 3
Cognition	Memory	No memory loss or slight inconstant forgetfulness	Consistent slight forgetfulness; partial recoll. of events; 'benign' forgetfulness X	Moderate memory loss; more marked for recent events; defect interferes with everyday activities	Severe memory loss; only highly learned material retained; new material rapidly lost	Severe memory loss; only fragments remain
	Orientation	Fully oriented X	Fully oriented except for slight difficulty with time relationships	Moderate difficulty with time relationships; oriented for place at examination; may have geographical disorientation elsewhere	Severe difficulty with time relationships; usually disoriented to time, often to place	Orientation to person only
	Judgement and problem-solving	Solves everyday problems and handles business and financial affairs well; judgement good in relation to past performance	Slight impairment in solving problems, similarities and differences X	Moderate difficulty in handling problems, similarities, and differences; social judgment usually maintained	Severely impaired in handling problems, similarities, and differences; social judgement usually impaired	Unable to make judgements or solve problems
Functioning	Community affairs	Independent function at usual level in job, shopping, and volunteer and social groups	Slight impairment in these activities	Unable to function independently at these activities although may still be engaged in some; appears normal to casual inspection X	No pretence of independent function outside the home	
	Home and hobbies	Life at home, hobbies, and intellectual interests well maintained	Life at home, hobbies, and intellectual interests slightly impaired	Mild but definite impairment of function at home; more difficult chores abandoned; more complicated hobbies and interests abandoned	Only simple chores preserved; very restricted interests, poorly maintained X	No significant function in home
	Personal care	Fully capable of self-care X		Needs prompting	Requires assistance in dressing, hygiene, keeping of personal effects	Requires much help with personal care; frequent incontinence

Figure 4: Possible degree of impairment across the 6 domains for a CSR-GS of 0.5 for moderate impairment of activities of daily living In this case, the CDR-SB is 4.0.

Appendix C Subgroup effects in the CLARITY AD study (lecanemab)

Clarity AD
CDR-SB stratified



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

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

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

Figure 5: Forest plots for the outcome symptoms (CDR-SB) – deterioration by ≥ 2.7 points at Month 18 of the CLARITY AD study (stratified analyses)[37]

Appendix D Comparison of the populations from the AACI and CLARITY AD studies

Table 16: Proportion of patients in the comparator arm with a 3-point deterioration in the CDR-SB at Month 18

AACI Population	Proportion of patients in the comparator arm ^a	CLARITY AD Population	Proportion of patients in the comparator arm ^a
without AChEI and CDR-GS = 0.5 or CDR-SB 0.5 to 4.0	21.5% or 22.2%	Untreated MCI	11.5% ^b
		Untreated mild Alzheimer's dementia	26.7% ^b
without AChEI and CDR-GS = 0.5 + with AChEI and CDR-GS = 1 or 2 or without AChEI and CDR-SB 0.5 to 4.0 + with AChEI and CDR-SB 4.5 to 9.0	29.5% ^c or 29.2% ^c	Research question 1 + Research question 2	19.3% ^b
a. Data without imputation of missing values (observed cases). b. Institute's calculation from data in Appendix C. c. Institute's calculation. AChEI: acetylcholinesterase inhibitor; CDR-GS: Clinical Dementia Rating-Global Score; CDR-SB: Clinical Dementia Rating-Sum of Boxes; MCI: mild cognitive impairment			

Appendix E Supplementary presentation of the iADRS results

E.1 Subpopulation with AChEI treatment and CDR-GS 1 or 2

Table 17: Results (morbidity, supplementary presentation) – RCT, direct comparison: donanemab + AChEI vs. placebo + AChEI (subpopulation with CDR-GS 1 or 2)

Study Outcome category Outcome	donanemab + AChEI		placebo + AChEI		donanemab + AChEI vs. placebo + AChEI
	N	Median time to event (weeks) [95% CI] Patients with event n (%)	N	Median time to event (weeks) [95% CI] Patients with event n (%)	HR [95% CI]; p-value ^a
AACI					
Morbidity					
<i>iADRS (time to permanent deterioration,^{b, c} supplementary presentation)</i>	122	80.0 [80.00; NC] 21 (17.2)	110	79.9 [77.00; NC] 30 (27.3)	0.76 [0.43; 1.33]
<i>ADCS-iADL (time to permanent deterioration,^{b, d} supplementary presentation)</i>	122	80.0 [77.00; NC] 33 (27.0)	110	77.4 [75.86; 79.86] 44 (40.0)	0.88 [0.55; 1.39]
<i>ADAS-Cog13 – time to permanent deterioration^{b, e}</i>	122	NA [78.14; NC] 20 (16.4)	110	79.9 [76.71; NC] 33 (30.0)	0.60 [0.34; 1.06]
a. Stratified Cox proportional hazards model with treatment, age, baseline value and use of AChEI at baseline as fixed effects, and the tau category at baseline as a stratification factor. b. A permanent deterioration was defined as the first point in time at which the relevant response criterion was met without any subsequent improvement until the end of the study, or when, following an initial (or, where applicable, confirmed) deterioration, only missing values occurred. c. A decrease of ≥ 21.6 points (15% of the scale range) from baseline is considered a clinically relevant deterioration (score range of the scale: 0 to 144). d. A decrease of ≥ 8.85 points (15% of the scale range) from baseline (score range of the scale: 0 to 59). No data are available on the total score (ADCS-ADL) or on the basic activities of daily living (ADCS-bADL), which would be necessary for interpreting the ADCS-iADL data. e. An increase of ≥ 12.75 points (15% of the scale range) from baseline is considered a clinically relevant deterioration (score range of the scale 0 to 85). AChEI: acetylcholinesterase inhibitor; ADAS-Cog13: Alzheimer's Disease Assessment Scale-Cognitive subscale 13-item version; ADCS-iADL: Alzheimer's Disease Cooperative Study-instrumental Activities of Daily Living subscale; CDR-GS: Clinical Dementia Rating-Global Score; CI: confidence interval; HR: hazard ratio; iADRS: integrated Alzheimer's Disease Rating Scale; n: number of patients with event; N: number of analysed patients; NC: not calculable; RCT: randomized controlled trial					

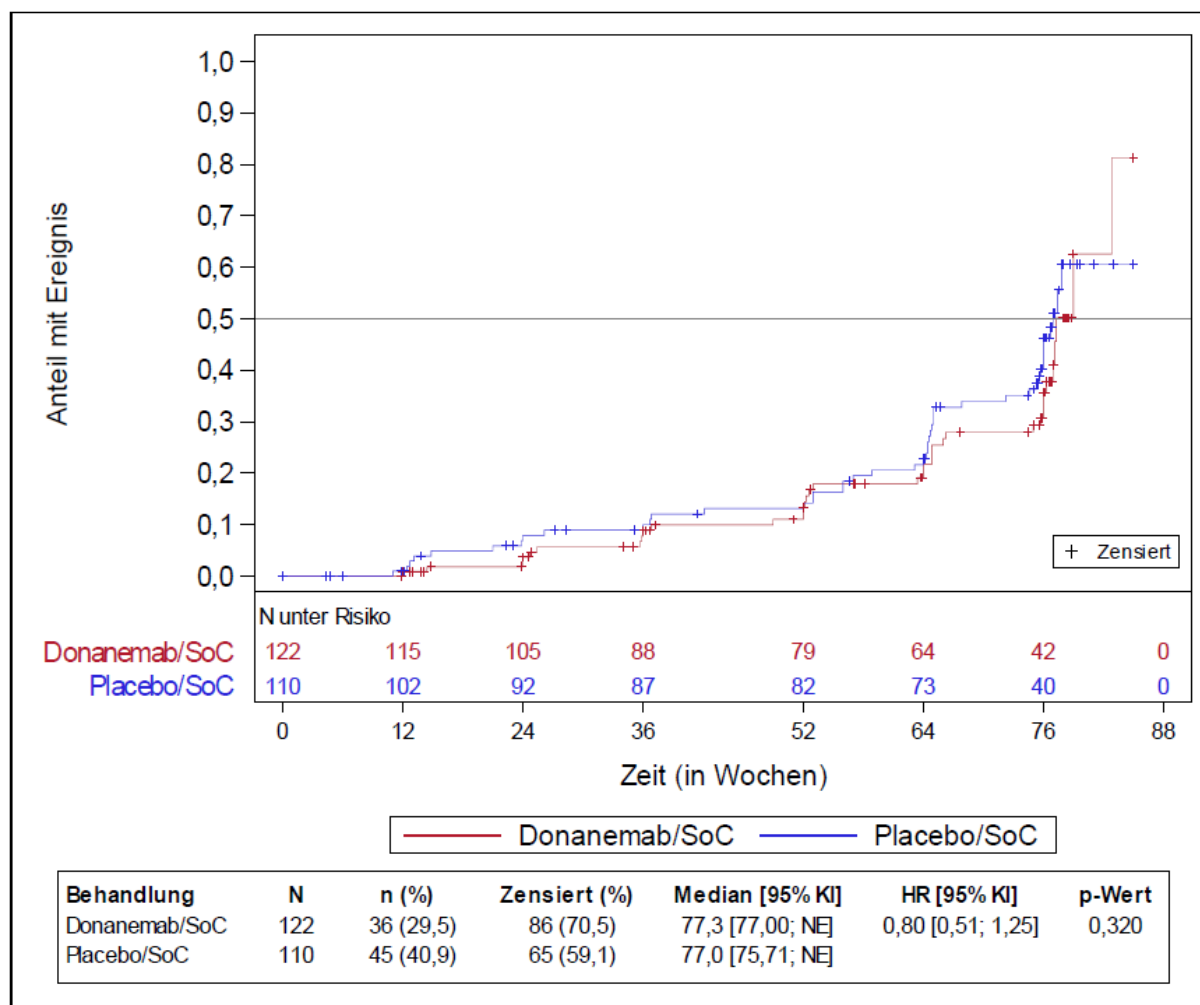
E.2 Subpopulations with AChEI treatment and CDR-SB 4.5 to 9 points

Table 18: Results (morbidity, supplementary presentation) – RCT, direct comparison: donanemab + AChEI vs. placebo + AChEI (subpopulation with CDR-SB 4.5 to 9)

Study Outcome category Outcome	donanemab + AChEI		placebo + AChEI		donanemab + AChEI vs. placebo + AChEI
	N	Median time to event (weeks) [95% CI] Patients with event n (%)	N	Median time to event (weeks) [95% CI] Patients with event n (%)	HR [95% CI]; p-value ^a
AACI					
Morbidity					
<i>iADRS (time to permanent deterioration^{b, c} supplementary presentation)</i>	119	80.0 [80.00; NC] 20 (16.8)	107	NA [77.00; NC] 26 (24.3)	0.77 [0.43; 1.39]
<i>ADCS-iADL (time to permanent deterioration^{b, d} supplementary presentation)</i>	119	80.0 [77.00; NC] 33 (27.7)	107	77.4 [76.57; NC] 39 (36.4)	0.88 [0.55; 1.41]
<i>ADAS-Cog13 – time to permanent deterioration^{b, e}</i>	119	NA [78.14; NC] 19 (16.0)	107	NA [76.71; NC] 30 (28.0)	0.56 [0.31; 0.9997]
a. Stratified Cox proportional hazards model with treatment, age, baseline value and use of AChEI at baseline as fixed effects, and the tau category at baseline as a stratification factor. b. A permanent deterioration was defined as the first point in time at which the relevant response criterion was met without any subsequent improvement until the end of the study, or when, following an initial (or, where applicable, confirmed) deterioration, only missing values occurred. d. A decrease of ≥ 8.85 points (15% of the scale range) from baseline (score range of the scale: 0 to 59). No data are available on the total score (ADCS-ADL) or on the basic activities of daily living (ADCS-bADL), which would be necessary for interpreting the ADCS-iADL data. e. An increase of ≥ 12.75 points (15% of the scale range) from baseline is considered a clinically relevant deterioration (score range of the scale 0 to 85). AChEI: acetylcholinesterase inhibitor; ADAS-Cog13: Alzheimer's Disease Assessment Scale-Cognitive subscale 13-item version; ADCS-iADL: Alzheimer's Disease Cooperative Study-instrumental Activities of Daily Living subscale; CDR-GS: Clinical Dementia Rating-Global Score; CI: confidence interval; HR: hazard ratio; iADRS: integrated Alzheimer's Disease Rating Scale; n: number of patients with an event; N: number of analysed patients; NC: not calculable; RCT: randomized controlled trial					

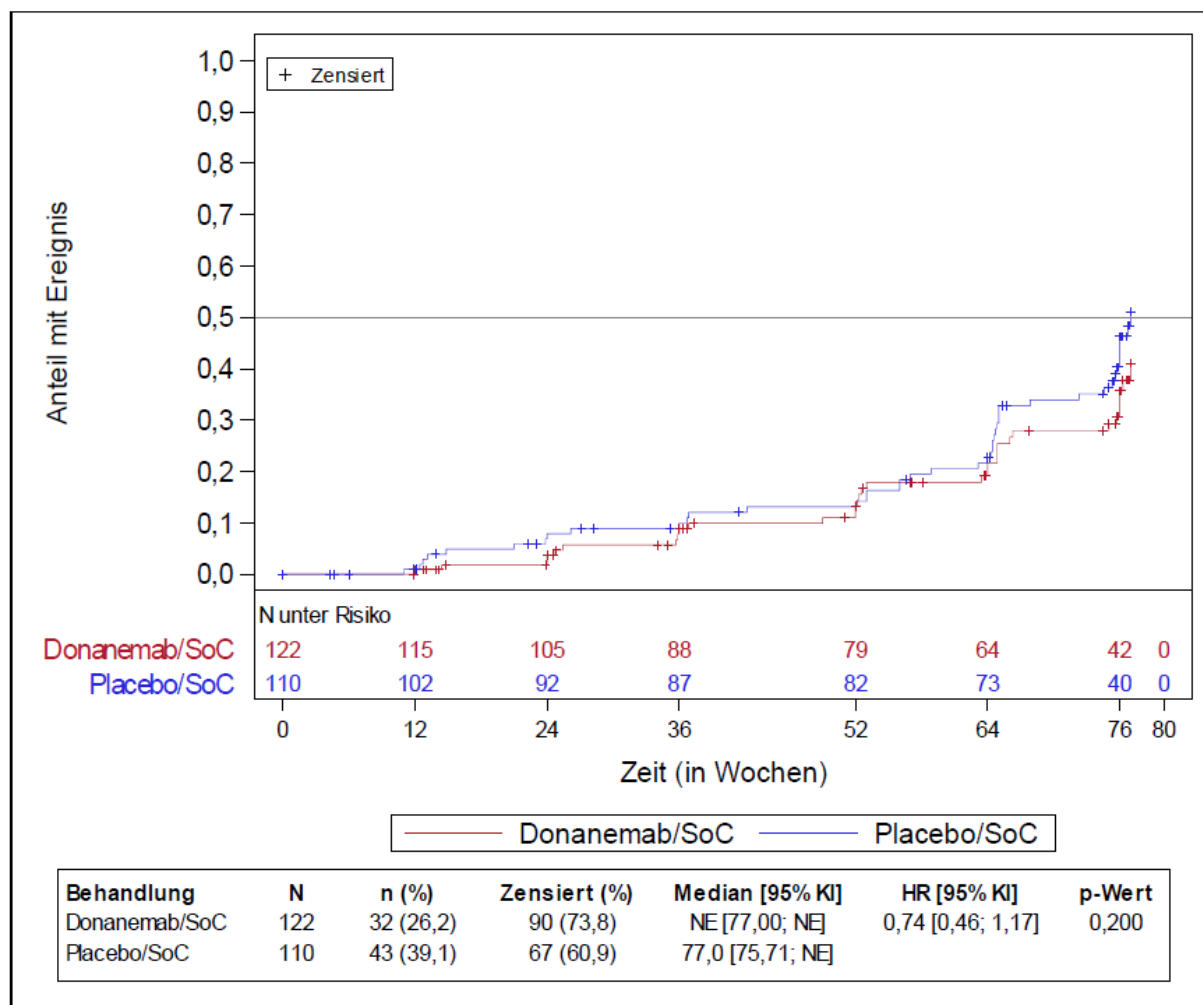
Appendix F Research question 2: Kaplan-Meier curves

F.1 Subpopulation with AChEI treatment and CDR-GS 1 or 2



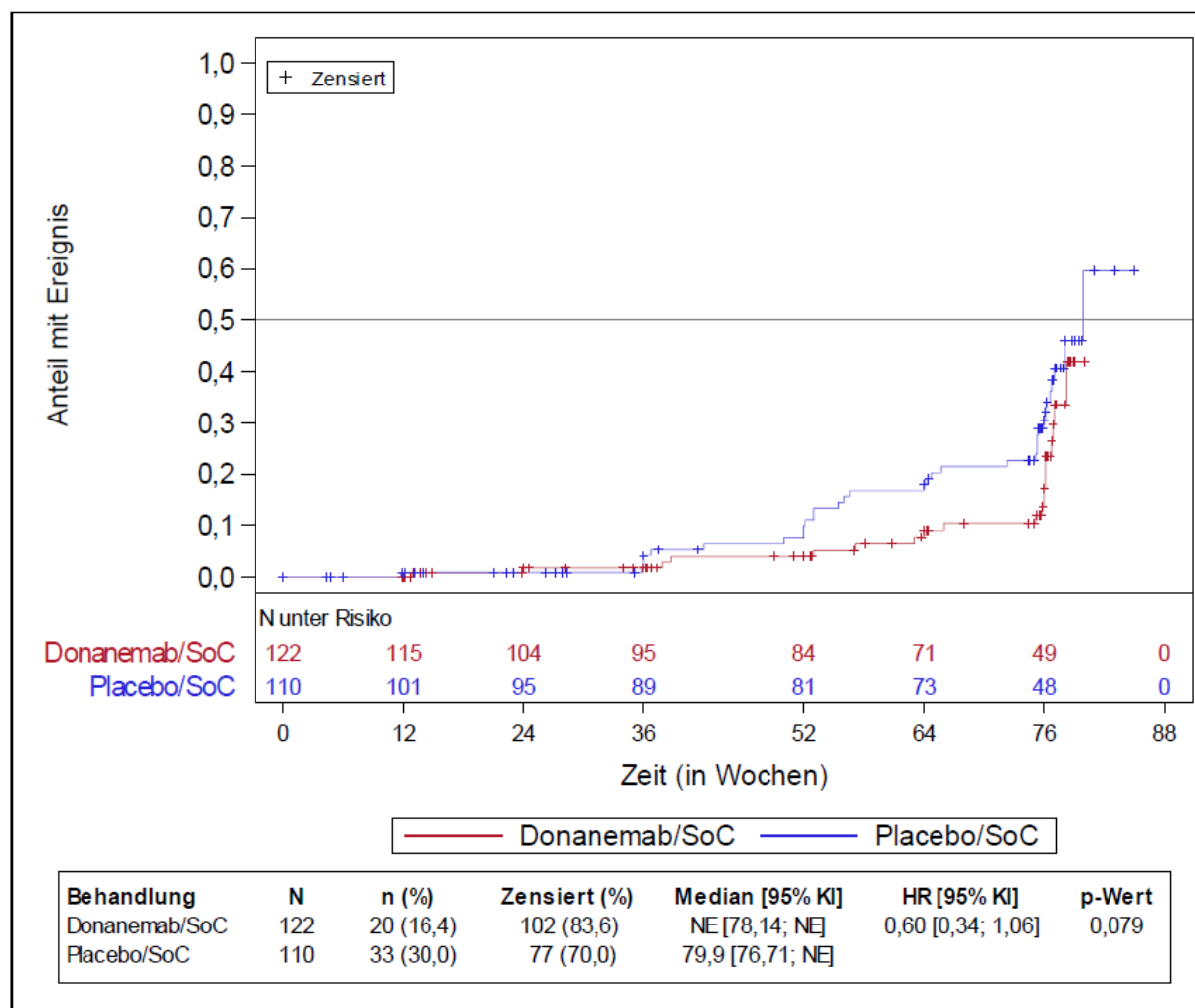
Anteil mit Ergebnis: proportion with event; Behandlung: treatment; N unter Risiko: N at risk; p-Wert: p-value; Zeit (in Wochen); time (in weeks); Zensiert: censored

Figure 6: Kaplan-Meier curves for the outcome symptoms (CDR-SB) in the AACI study – time to permanent deterioration; subpopulation with AChEI treatment and CDR-GS 1 or 2



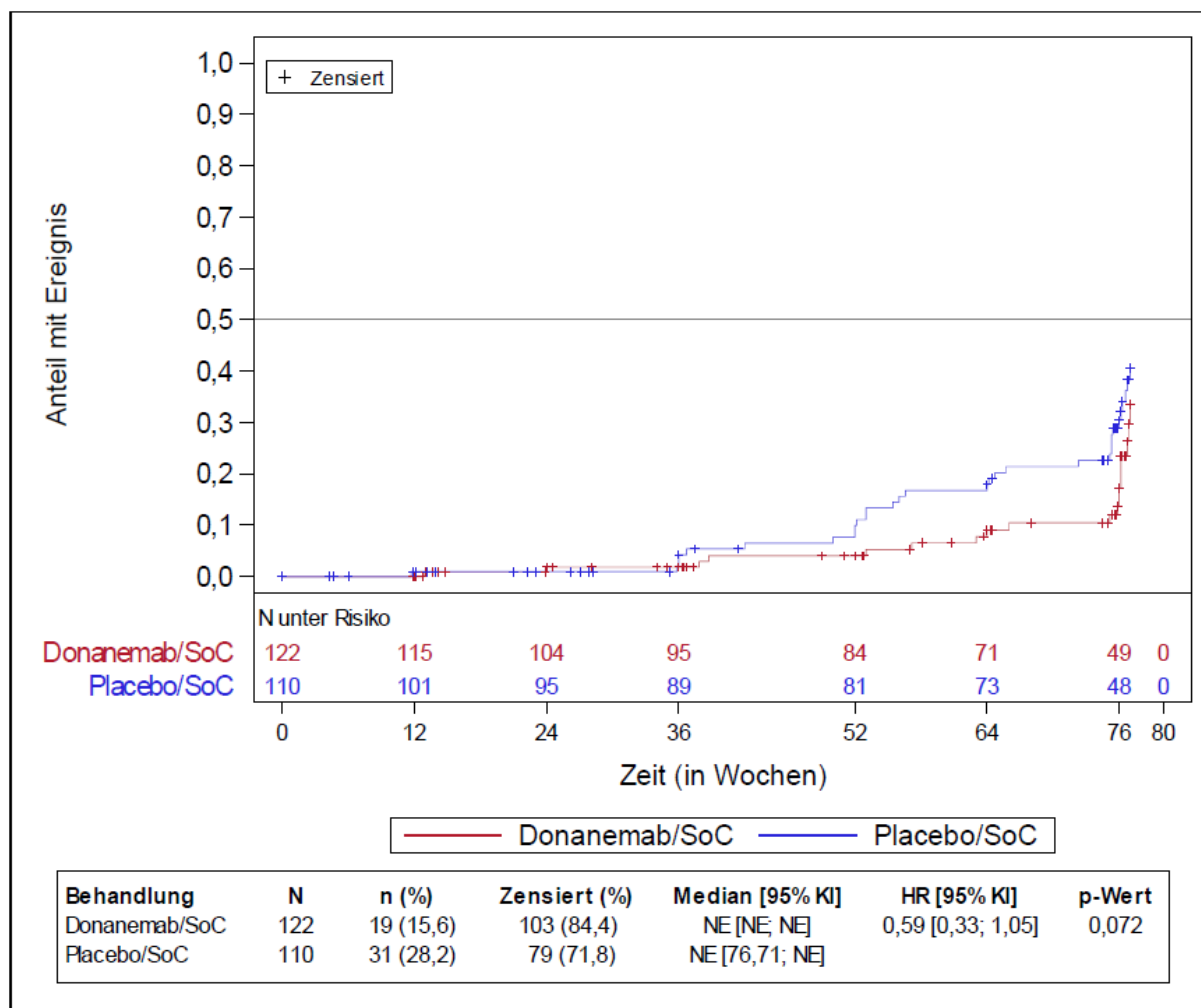
Anteil mit Ergebnis: proportion with event; Behandlung: treatment; N unter Risiko: N at risk; p-Wert: p-value; Zeit (in Wochen); time (in weeks); Zensiert: censored

Figure 7: Kaplan-Meier curves for the outcome symptoms (CDR-SB) in the AACI study – time to permanent deterioration; subpopulation with AChEI treatment and CDR-GS 1 or 2; sensitivity analyses: data after Day 533 + 7 days not included (supplementary presentation)



Anteil mit Ergebnis: proportion with event; Behandlung: treatment; N unter Risiko: N at risk; p-Wert: p-value; Zeit (in Wochen); time (in weeks); Zensiert: censored

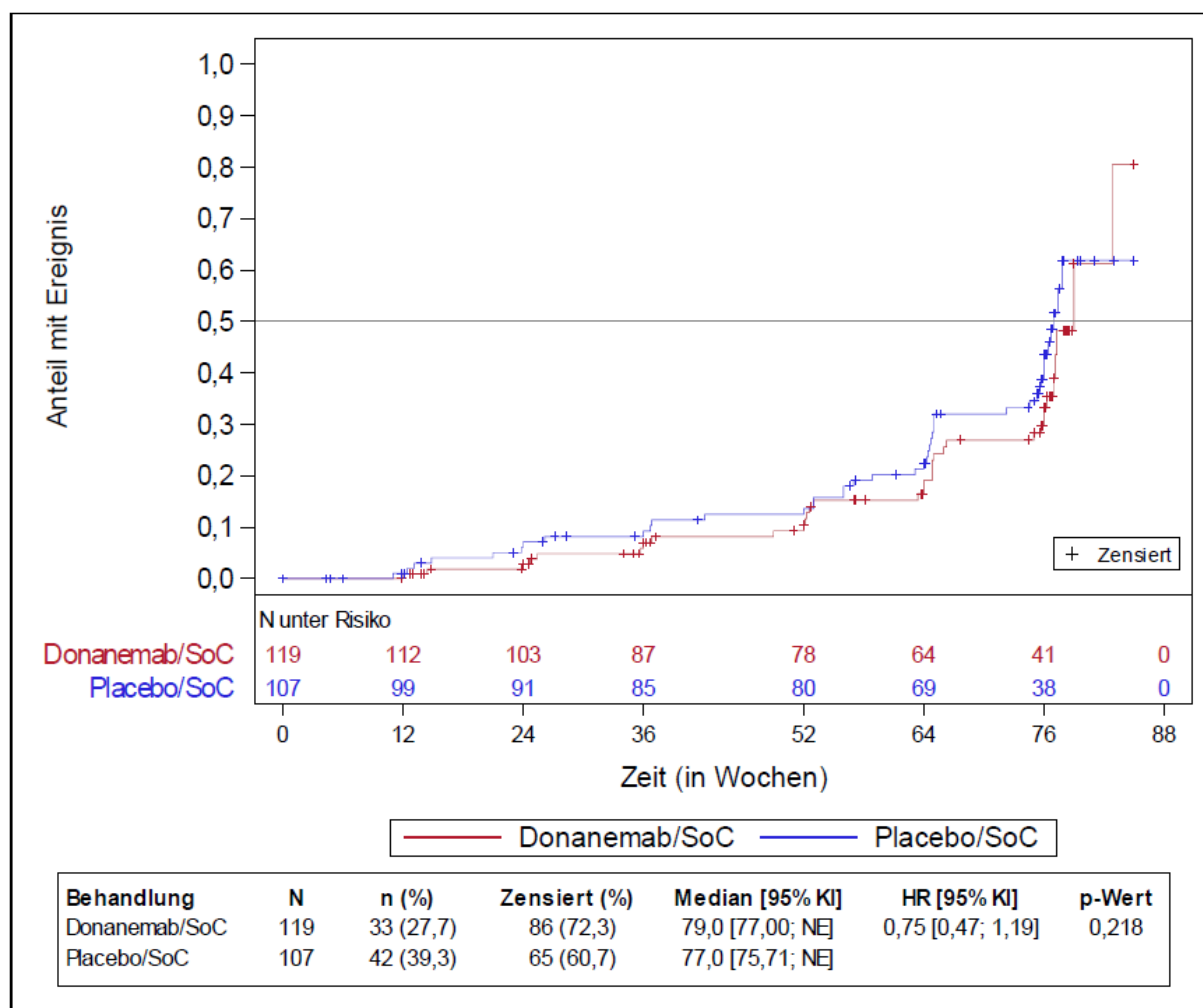
Figure 8: Kaplan-Meier curves for the outcome cognition (ADAS-Cog13) in the AACI study – time to permanent deterioration; subpopulation with AChEI treatment and CDR-GS 1 or 2



Anteil mit Ergebnis: proportion with event; Behandlung: treatment; N unter Risiko: N at risk; p-Wert: p-value; Zeit (in Wochen); time (in weeks); Zensiert: censored

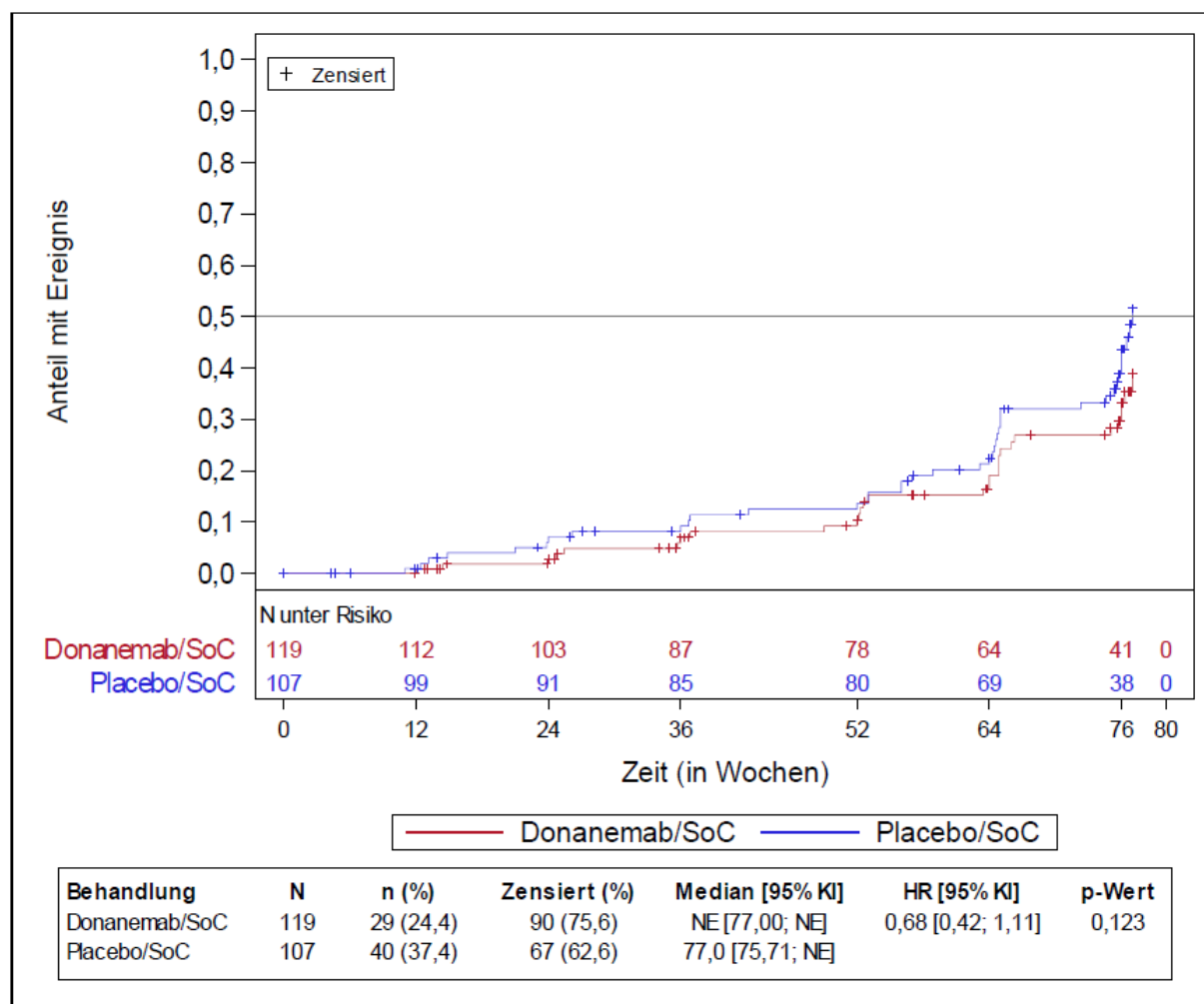
Figure 9: Kaplan-Meier curves for the outcome cognition (ADAS-Cog13) in the AACI study – time to permanent deterioration; subpopulation with AChEI treatment and CDR-GS 1 or 2; sensitivity analyses: data after Day 533 + 7 days not included (supplementary presentation)

F.2 Subpopulations with AChEI treatment and CDR-SB 4.5 to 9 points



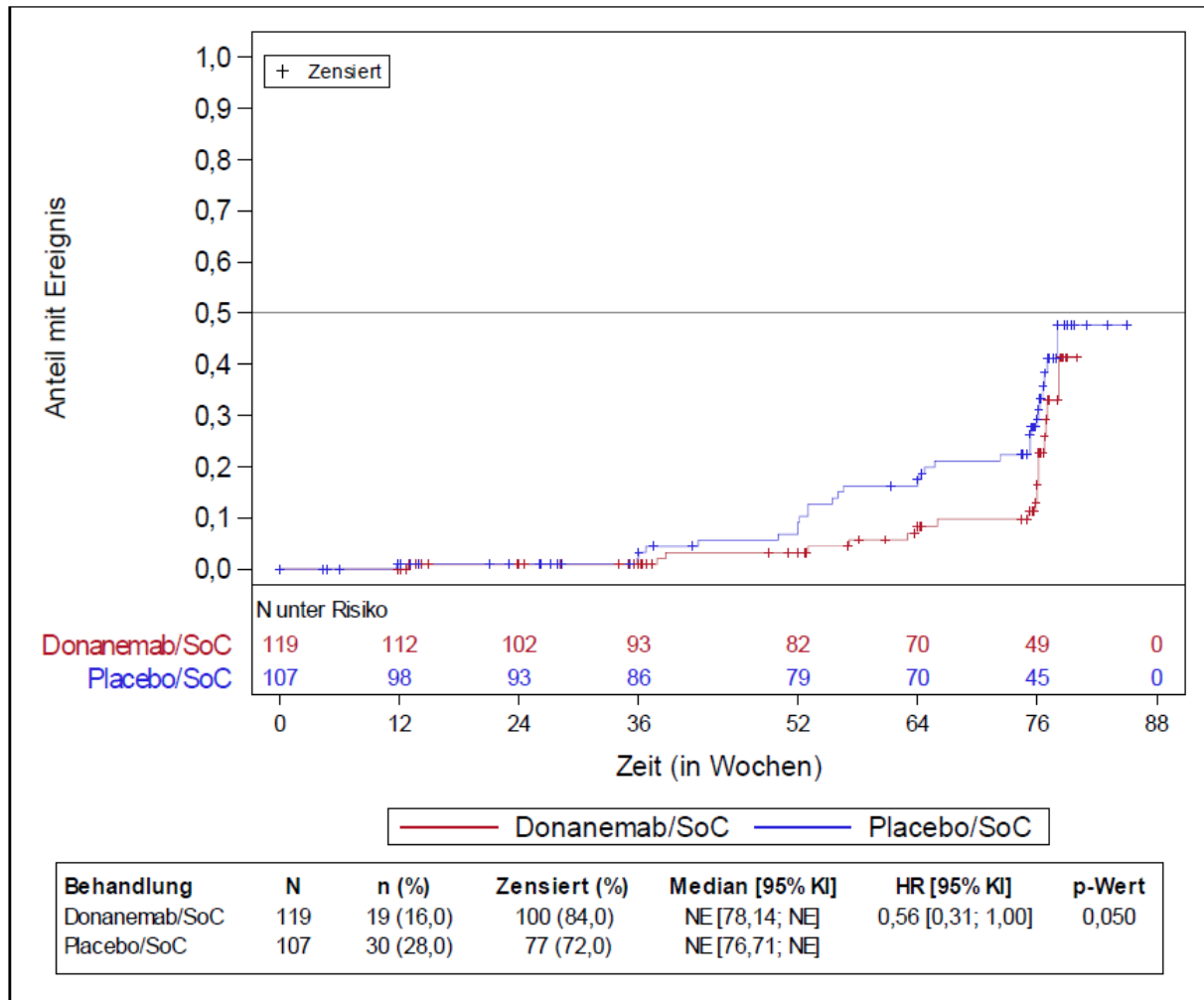
Anteil mit Ergebnis: proportion with event; Behandlung: treatment; N unter Risiko: N at risk; p-Wert: p-value; Zeit (in Wochen); time (in weeks); Zensiert: censored

Figure 10: Kaplan-Meier curves for the outcome symptoms (CDR-SB) in the AACI study – time to permanent deterioration; subpopulation with AChEI treatment and CDR-SB 4.5 to 9



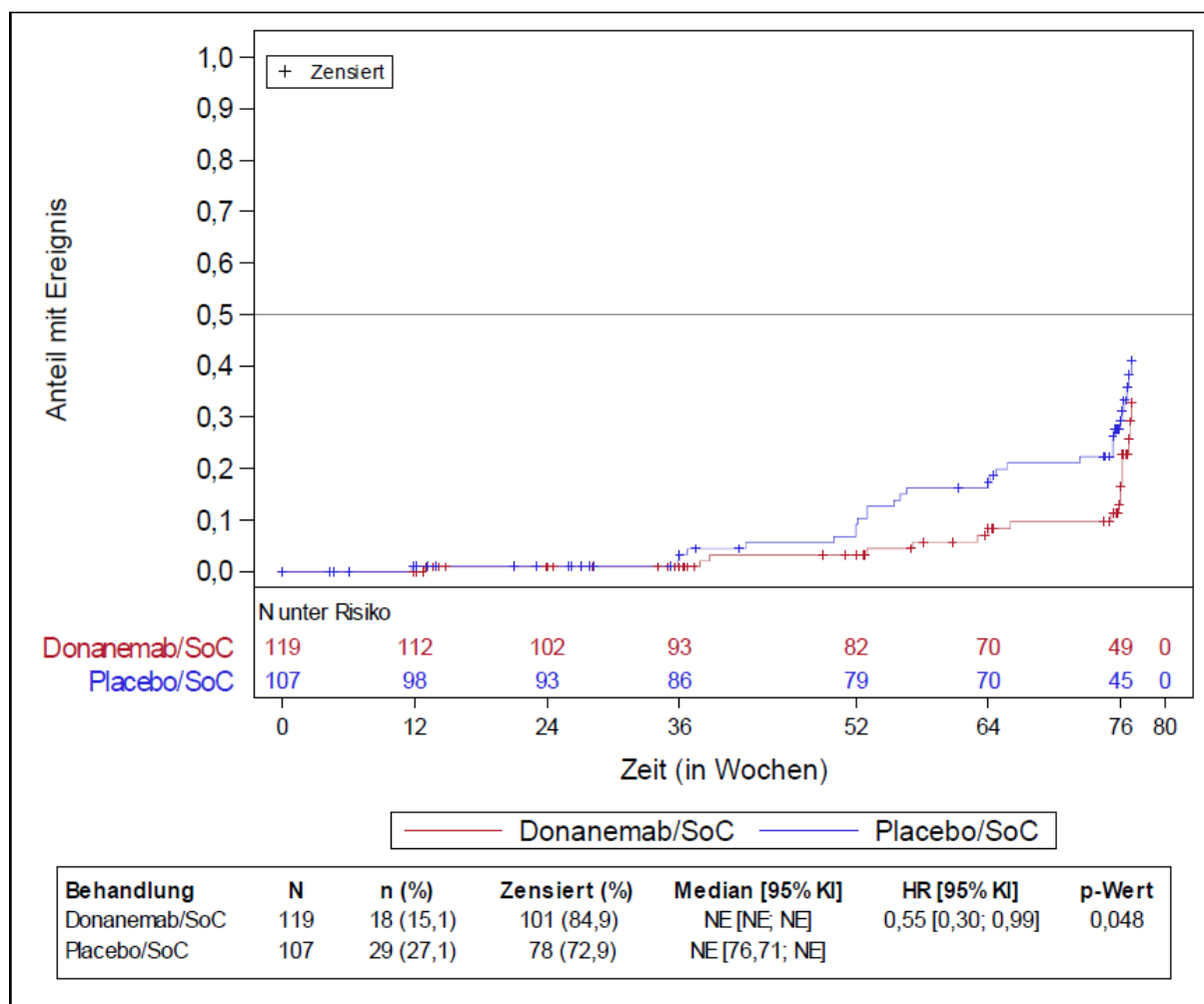
Anteil mit Ergebnis: proportion with event; Behandlung: treatment; N unter Risiko: N at risk; p-Wert: p-value; Zeit (in Wochen); time (in weeks); Zensiert: censored

Figure 11: Kaplan-Meier curves for the outcome symptoms (CDR-SB) in the AACI study – time to permanent deterioration; subpopulation with AChEI treatment and CDR-SB 4.5 to 9; sensitivity analyses: data after Day 533 + 7 days not included (supplementary presentation)



Anteil mit Ergebnis: proportion with event; Behandlung: treatment; N unter Risiko: N at risk; p-Wert: p-value; Zeit (in Wochen): time (in weeks); Zensiert: censored

Figure 12: Kaplan-Meier curves for the outcome cognition (ADAS-Cog13) in the AACI study – time to permanent deterioration; subpopulation with AChEI treatment CDR-SB 4.5 to 9



Anteil mit Ergebnis: proportion with event; Behandlung: treatment; N unter Risiko: N at risk; p-Wert: p-value; Zeit (in Wochen); time (in weeks); Zensiert: censored

Figure 13: Kaplan-Meier curves for the outcome cognition (ADAS-Cog13) in the AACI study – time to permanent deterioration; subpopulation with AChEI treatment and CDR-SB 4.5 to 9; sensitivity analyses: data after Day 533 + 7 days not included (supplementary presentation)

Appendix G Research question 2: Results on side effects

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

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

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

G.1 Subpopulation with AChEI treatment and CDR-GS 1 or 2

Table 19: Common AEs^a – RCT, direct comparison: donanemab + AChEI vs. placebo + AChEI (subpopulations with CDR-GS 1 or 2)

Study SOC ^b PT ^b	Patients with event n (%)	
	donanemab + AChEI N = 120	placebo + AChEI N = 110
AACI		
Overall AE rate	107 (89.2)	90 (81.8)
Cardiac disorders	12 (10.0)	6 (5.5)
Gastrointestinal disorders	30 (25.0)	20 (18.2)
General disorders and administration site conditions	23 (19.2)	16 (14.5)
Infections and infestations	44 (36.7)	43 (39.1)
COVID-19	16 (13.3)	16 (14.5)
Injury, poisoning and procedural complications	31 (25.8)	29 (26.4)
Fall	15 (12.5)	11 (10.0)
Investigations	21 (17.5)	7 (6.4)
Metabolism and nutrition disorders	18 (15.0)	7 (6.4)
Musculoskeletal and connective tissue disorders	26 (21.7)	21 (19.1)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	11 (9.2)	7 (6.4)
Nervous system disorders	55 (45.8)	34 (30.9)
Amyloid related imaging abnormality-microhaemorrhages and haemosiderin deposits	25 (20.8)	9 (8.2)
Amyloid related imaging abnormality-oedema/effusion	20 (16.7)	0 (0.0)
Headache	12 (10.0)	9 (8.2)
Psychiatric disorders	39 (32.5)	26 (23.6)
Renal and urinary disorders	15 (12.5)	6 (5.5)
Respiratory, thoracic and mediastinal disorders	13 (10.8)	9 (8.2)
Skin and subcutaneous tissue disorders	17 (14.2)	9 (8.2)
Vascular disorders	17 (14.2)	18 (16.4)
a. Events that occurred in ≥ 10 patients in at least one study arm. b. MedDRA version 25.1; SOC and PT notation taken without adaptation from the comments. AChEI: acetylcholinesterase inhibitor; AE: adverse event; CDR-GS: Clinical Dementia Rating-Global Score; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with at least one event; N: number patients who received at least one dose of study medication; PT: Preferred Term; RCT: randomized controlled trial; SOC: System Organ Class		

Table 20: Common SAEs^a – RCT, direct comparison: donanemab + AChEI vs. placebo + AChEI, subpopulations with CDR-GS 1 or 2

Study SOC ^b	Patients with event n (%)	
	donanemab + AChEI N = 120	placebo + AChEI N = 110
AACI		
Overall SAE rate	27 (22.5)	17 (15.5)
Infections and infestations	7 (5.8)	2 (1.8)
Nervous system disorders	6 (5.0)	4 (3.6)
a. Events that occurred in ≥ 5% of patients in at least one study arm. b. MedDRA version 25.1; SOC notation taken without adaptation from the comments. AChEI: acetylcholinesterase inhibitor; CDR-GS: Clinical Dementia Rating-Global Score; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with at least one event; N: number patients who received at least one dose of study medication; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class		

Table 21: Discontinuations due to AEs – RCT, direct comparison: donanemab + AChEI vs. placebo + AChEI, subpopulations with CDR-GS 1 or 2 (multipage table)

Study SOC ^a PT ^a	Patients with event n (%)	
	donanemab + AChEI N = 120	placebo + AChEI N = 110
AACI		
Overall rate of discontinuations due to AEs	20 (16.7)	6 (5.5)
Gastrointestinal disorders	1 (0.8)	0 (0)
Retroperitoneal haemorrhage	1 (0.8)	0 (0)
Immune system disorders	1 (0.8)	0 (0)
Infusion related hypersensitivity reaction	1 (0.8)	0 (0)
Infections and infestations	1 (0.8)	0 (0)
COVID-19	1 (0.8)	0 (0)
Injury, poisoning and procedural complications	4 (3.3)	2 (1.8)
Infusion related reaction	4 (3.3)	0 (0)
Respiratory fume inhalation disorder	0 (0)	1 (0.9)
Spinal compression fracture	0 (0)	1 (0.9)
Investigations	1 (0.8)	0 (0)
Hepatic enzyme increased	1 (0.8)	0 (0)

Table 21: Discontinuations due to AEs – RCT, direct comparison: donanemab + AChEI vs. placebo + AChEI, subpopulations with CDR-GS 1 or 2 (multipage table)

Study SOC ^a PT ^a	Patients with event n (%)	
	donanemab + AChEI N = 120	placebo + AChEI N = 110
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	3 (2.5)	1 (0.9)
Chronic lymphocytic leukaemia	1 (0.8)	0 (0)
Lung adenocarcinoma stage IV	1 (0.8)	0 (0)
Plasma cell myeloma	1 (0.8)	0 (0)
Rectal cancer	0 (0)	1 (0.9)
Nervous system disorders	5 (4.2)	1 (0.9)
Amyloid related imaging abnormality-microhaemorrhages and haemosiderin deposits	2 (1.7)	0 (0)
Amyloid related imaging abnormality-oedema/effusion	1 (0.8)	0 (0)
Dementia Alzheimer's type	1 (0.8)	0 (0)
Ischaemic stroke	0	1 (0.9)
Superficial siderosis of the central nervous system	1 (0.8)	0 (0)
Psychiatric disorders	1 (0.8)	0 (0)
Agitation	1 (0.8)	0 (0)
Renal and urinary disorders	0 (0)	1 (0.9)
Chronic kidney disease	0 (0)	1 (0.9)
Respiratory, thoracic and mediastinal disorders	2 (1.7)	0 (0)
Pulmonary embolism	1 (0.8)	0 (0)
Respiratory arrest	1 (0.8)	0 (0)
Vascular disorders	1 (0.8)	1 (0.9)
Hypotension	1 (0.8)	0 (0)
Vein rupture	0 (0)	1 (0.9)
a. MedDRA version 25.1; SOC and PT notation taken without adaptation from the comments. AChEI: acetylcholinesterase inhibitor; AE: adverse event; CDR-GS: Clinical Dementia Rating-Global Score; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with at least one event; N: number patients who received at least one dose of study medication; PT: Preferred Term; RCT: randomized controlled trial; SOC: System Organ Class		

G.2 Subpopulations with AChEI treatment and CDR-SB 4.5 to 9 points

Table 22: Common AEs^a – RCT, direct comparison: donanemab + AChEI vs. placebo + AChEI, subpopulations with CDR-SB 4.5 to 9

Study SOC ^b PT ^b	Patients with event n (%)	
	donanemab + AChEI N = 117	placebo + AChEI N = 107
AACI		
Overall AE rate	105 (89.7)	84 (78.5)
Cardiac disorders	12 (10.3)	6 (5.6)
Gastrointestinal disorders	30 (25.6)	21 (19.6)
General disorders and administration site conditions	21 (17.9)	15 (14.0)
Infections and infestations	44 (37.6)	39 (36.4)
COVID-19	18 (15.4)	14 (13.1)
Injury, poisoning and procedural complications	32 (27.4)	27 (25.2)
Fall	15 (12.8)	9 (8.4)
Investigations	18 (15.4)	8 (7.5)
Metabolism and nutrition disorders	20 (17.1)	8 (7.5)
Musculoskeletal and connective tissue disorders	27 (23.1)	19 (17.8)
Nervous system disorders	57 (48.7)	32 (29.9)
Amyloid related imaging abnormality-microhaemorrhages and haemosiderin deposits	26 (22.2)	8 (7.5)
Amyloid related imaging abnormality-oedema/effusion	22 (18.8)	0 (0.0)
Headache	13 (11.1)	9 (8.4)
Psychiatric disorders	39 (33.3)	25 (23.4)
Renal and urinary disorders	14 (12.0)	6 (5.6)
Respiratory, thoracic and mediastinal disorders	14 (12.0)	9 (8.4)
Skin and subcutaneous tissue disorders	16 (13.7)	11 (10.3)
Vascular disorders	17 (14.5)	17 (15.9)
a. Events that occurred in ≥ 10 patients in at least one study arm.		
b. MedDRA version 25.1; SOC and PT notation taken without adaptation from the comments.		
AChEI: acetylcholinesterase inhibitor; AE: adverse event; CDR-SB: Clinical Dementia Rating-Sum of Boxes; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with at least one event; N: number patients who received at least one dose of study medication; PT: Preferred Term; RCT: randomized controlled trial; SOC: System Organ Class		

Table 23: Common SAEs^a – RCT, direct comparison: donanemab + AChEI vs. placebo + AChEI, subpopulations with CDR-SB 4.5 to 9

Study SOC ^b	Patients with event n (%)	
	donanemab + AChEI N = 117	placebo + AChEI N = 107
AACI		
Overall SAE rate	25 (21.4)	16 (15.0)
Infections and infestations	7 (6.0)	2 (1.9)
Nervous system disorders	6 (5.1)	3 (2.8)
a. Events that occurred in ≥ 5% of patients in at least one study arm. b. MedDRA version 25.1; SOC notation taken without adaptation from the comments. AChEI: acetylcholinesterase inhibitor; CDR-SB: Clinical Dementia Rating-Sum of Boxes; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with at least one event; N: number patients who received at least one dose of study medication; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class		

Table 24: Discontinuations due to AEs – RCT, direct comparison: donanemab + AChEI vs. placebo + AChEI, subpopulations with CDR-SB 4.5 to 9 (multipage table)

Study SOC ^a PT ^a	Patients with event n (%)	
	donanemab + AChEI N = 117	placebo + AChEI N = 107
AACI		
Overall rate of discontinuations due to AEs	19 (16.2)	5 (4.7)
Gastrointestinal disorders	1 (0.9)	0 (0)
Retroperitoneal haemorrhage	1 (0.9)	0 (0)
Infections and infestations	1 (0.9)	0 (0)
COVID-19	1 (0.9)	0 (0)
Injury, poisoning and procedural complications	4 (3.4)	2 (1.9)
Infusion related reaction	4 (3.4)	0 (0)
Respiratory fume inhalation disorder	0 (0)	1 (0.9)
Spinal compression fracture	0 (0)	1 (0.9)
Investigations	1 (0.9)	0 (0)
Hepatic enzyme increased	1 (0.9)	0 (0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	2 (1.7)	1 (0.9)
Lung adenocarcinoma stage IV	1 (0.9)	0 (0)
Plasma cell myeloma	1 (0.9)	0 (0)
Rectal cancer	0 (0)	1 (0.9)

Table 24: Discontinuations due to AEs – RCT, direct comparison: donanemab + AChEI vs. placebo + AChEI, subpopulations with CDR-SB 4.5 to 9 (multipage table)

Study SOC ^a PT ^a	Patients with event n (%)	
	donanemab + AChEI N = 117	placebo + AChEI N = 107
Nervous system disorders	6 (5.1)	0 (0)
Amyloid related imaging abnormality-microhaemorrhages and haemosiderin deposits	2 (1.7)	0 (0)
Amyloid related imaging abnormality-oedema/effusion	2 (1.7)	0 (0)
Dementia Alzheimer's type	1 (0.9)	0 (0)
Superficial siderosis of the central nervous system	1 (0.9)	0 (0)
Psychiatric disorders	1 (0.9)	0 (0)
Agitation	1 (0.9)	0 (0)
Renal and urinary disorders	0 (0)	1 (0.9)
Chronic kidney disease	0 (0)	1 (0.9)
Respiratory, thoracic and mediastinal disorders	2 (1.7)	0 (0)
Pulmonary embolism	1 (0.9)	0 (0)
Respiratory arrest	1 (0.9)	0 (0)
Vascular disorders	1 (0.9)	1 (0.9)
Hypotension	1 (0.9)	0 (0)
Vein rupture	0 (0)	1 (0.9)
a. MedDRA version 25.1; SOC and PT notation taken without adaptation from the comments. AChEI: acetylcholinesterase inhibitor; AE: adverse event; CDR-SB: Clinical Dementia Rating-Sum of Boxes; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with at least one event; N: number patients who received at least one dose of study medication; PT: Preferred Term; RCT: randomized controlled trial; SOC: System Organ Class		