

Donanemab (early Alzheimer's disease)

Benefit assessment according to §35a SGB V¹

A horizontal bar composed of 20 small squares in various shades of blue and grey. A larger, solid dark blue rectangle is overlaid on the bar, containing the word 'EXTRACT' in white capital letters.

EXTRACT

Project: A25-134

Version: 1.0

Status: 28 Jan 2026

DOI: 10.60584/A25-134_en

¹ Translation of Sections I 1 to I 6 of the dossier assessment *Donanemab (frühe Alzheimer-Krankheit)* – *Nutzenbewertung gemäß § 35a SGB V*. Please note: This translation is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

Publishing details

Publisher

Institute for Quality and Efficiency in Health Care

Topic

Donanemab (early Alzheimer's disease) – Benefit assessment according to §35a SGB V

Commissioning agency

Federal Joint Committee

Commission awarded on

22 October 2025

Internal Project No.

A25-134

DOI-URL

https://doi.org/10.60584/A25-134_en

Address of publisher

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Recommended citation

Institute for Quality and Efficiency in Health Care. Donanemab (early Alzheimer's disease); Benefit assessment according to §35a SGB V; Extract [online]. 2026 [Accessed: DD.MM.YYYY]. URL: https://doi.org/10.60584/A25-134_en.

Keywords

Donanemab, Alzheimer Disease, Benefit Assessment, NCT04437511

Medical and scientific advice

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

Patient and family involvement

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

IQWiG thanks the respondent and the patient organization 'Deutsche Alzheimer Gesellschaft e. V.' for participating in the written exchange and for their support. The respondent and the 'Deutsche Alzheimer Gesellschaft e. V.' were not involved in the actual preparation of the dossier assessment.

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Part I: Benefit assessment

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² Table numbers start with “2” as numbering follows that of the full dossier assessment.

I List of abbreviations

Abbreviation	Meaning
AChEI	acetylcholinesterase inhibitor
ACT	appropriate comparator therapy
ADAS-Cog	Alzheimer's Disease Assessment Scale-Cognitive subscale
ADCS-iADL	Alzheimer's Disease Cooperative Study-instrumental Activities of Daily Living subscale
AE	adverse event
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-GS	Clinical Dementia Rating-Global Score
CDR-SB	Clinical Dementia Rating-Sum of Boxes
CERAD-plus	Consortium to Establish a Registry for Alzheimer's Disease
CTCAE	Common Terminology Criteria for Adverse Events
EMA	European Medicines Agency
FDA	Food and Drug Administration
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)
LLT	Lowest Level Term
MCI	mild cognitive impairment
MedDRA	Medical Dictionary for Regulatory Activities
MMSE	Mini-Mental State Examination
MoCA	Montreal Cognitive Assessment
MRI	magnetic resonance imaging
OECD	Organisation for Economic Co-operation and Development
PET	positron emission tomography
RCT	randomized controlled trial
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SmPC	summary of product characteristics

I 1 Executive summary of the benefit assessment

Background

In accordance with §35a Social Code Book V, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the drug donanemab. The assessment is based on a dossier compiled by the pharmaceutical company (hereinafter referred to as the ‘company’). The dossier was sent to IQWiG on 22 October 2025.

Research question

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

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

Table 2: 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 company followed the G-BA’s specification of the ACT for the research questions, divided into MCI and mild dementia, in each case caused by Alzheimer’s disease. In Module 4 A, however, the company addressed a 3rd research question in addition to the G-BA’s 2 research questions, in which the populations covered by the G-BA’s 2 research questions were pooled into a total population, which the company referred to as the ‘total target population’ and

described as 'adult patients with early symptomatic Alzheimer's disease'. The population formed by the company for this 3rd research question is referred to below as the Module 4 A total population. The company cited as the reason for this approach what it saw as a lack of clarity in the definition of the stages of Alzheimer's disease. For this 3rd research question, the company identified 'individualized treatment that takes into account disease progression along the Alzheimer's disease continuum and involves a choice between watchful waiting and the use of acetylcholinesterase inhibitors (AChEIs)' as the ACT. This approach had no bearing on the completeness of the study pool. The assessment of the added benefit was conducted in comparison with the G-BA's ACT presented in Table 2.

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

Study pool and study design

AACI study

Concurring with the company, the AACI study was included in the benefit assessment. However, the subpopulations defined by the company in relation to the research questions set out in Table 2 were not appropriate and could not be used for the benefit assessment. Uncertainty remains as to whether it is possible, on the basis of the data collected in the study, to distinguish adequately between patients with MCI and those with mild Alzheimer's dementia.

The AACI study is a randomized, double-blind study on the comparison of donanemab with placebo. The study included patients aged between 60 and 85 years who had experienced a gradual and progressive change in memory function for at least 6 months and had a Mini-Mental State Examination (MMSE) score of at least 20 and no more than 28 points, and who met the positron emission tomography (PET) scan criteria for the presence of amyloid pathology and tau pathology. The case report form required the patient to be identified as having Alzheimer's disease. There were no further inclusion criteria regarding a diagnosis of MCI due to Alzheimer's disease or early Alzheimer's dementia. Patients with other neurological disorders of the central nervous system were excluded from the study if these conditions might impair cognition or ability to participate in the study; these included, amongst others, other forms of dementia and Parkinson's disease. Patients with other psychiatric disorders were also excluded from participation if, in the opinion of the investigator, these disorders could interfere with their participation in the study, cognitive testing or the interpretation of the treatment effect; this included, amongst other things, schizophrenia. Patients were also excluded from the study if they had clinically important

abnormalities or if the results of their screening magnetic resonance imaging (MRI) suggested another potential aetiology of dementia.

A total of 1736 patients were enrolled in AACI, regardless of their ApoE ϵ 4 status, and were randomly assigned to receive donanemab (N = 860) or placebo (N = 876). Allocation was stratified by study centre and tau pathology (intermediate/high).

Concomitant drug treatment for Alzheimer's disease could be continued provided that it had been administered at a stable dose for at least 30 days prior to the start of the study. Where medically indicated, dose modifications could be conducted. Initiation or termination of this drug therapy during the course of the study was also allowed if medically indicated. Non-drug treatment of Alzheimer's disease was permitted, subject to the same restrictions as drug therapy. In the AACI study, treatment with donanemab was not fully in compliance with the summary of product characteristics (SmPC). Initially, a dose of 1400 mg was planned from the start of the study. In accordance with the protocol amendment, the first 3 doses were each 700 mg.

The primary outcome of the study was the change in the Integrated Alzheimer's Disease Rating Scale (iADRS) up to Week 76.

Limitations of the AACI study

The AACI study was included in the benefit assessment (in accordance with the company), as it included patients relevant to the research questions at hand, notwithstanding the inappropriately defined subpopulations that the company identified. The key limitations listed below do not, on the whole, call into question the relevance of the study:

- Uncertainties regarding the population: The presence of Alzheimer's disease in general, or the presence of MCI due to Alzheimer's disease / the presence of mild Alzheimer's dementia in particular, were not specified as inclusion criteria. The AACI study did not ensure the exclusion of patients who do not yet meet the criteria for MCI, or of patients with moderate Alzheimer's dementia.
- Missing data on the use of the AChEI therapy: No information was available regarding dosages or the timing of modifications to AChEI therapy. However, this information would be necessary in order to check whether the drugs of the ACT were also administered in compliance with the SmPC.
- Lack of guidelines on how to deal with a lack of efficacy or progression to the next stage:
 - According to the SmPC, donanemab is approved for the treatment of MCI and mild dementia, both caused by Alzheimer's disease. If the disease progresses to the moderate stage, treatment must be discontinued before the end of the maximum treatment duration of 18 months. Discontinuation of treatment with donanemab in

case of progression to the moderate stage was not planned for in the study. If continued treatment with donanemab were to occur in the moderate stage, this would constitute off-label use. The study did not include an overall assessment by the doctors regarding progression or the transition to moderate Alzheimer's dementia. The proportion of patients with progression to moderate Alzheimer's dementia and thus an indication for discontinuation was therefore unclear.

- Regular assessment of cognitive functioning and clinical symptoms is recommended for both donanemab and AChEIs. Among other things, this review is intended to help determine whether treatment should be discontinued if there is a lack of clinical efficacy. An overall assessment by the physicians regarding a lack of effectiveness, with corresponding requirements to discontinue donanemab or AChEIs, was not allowed for. The study protocol stipulated that existing AChEI treatment should be continued as far as possible without change. Modifications to the therapy were to be avoided, but could be made if medically necessary. The company did not provide any reasons for the therapy adjustments. It was therefore unclear whether the AChEIs were discontinued due to a lack of therapeutic effectiveness or whether treatment with another drug was possibly initiated.
- AChEIs are approved for the treatment of mild and moderate Alzheimer's dementia. According to the guidelines, patients with MCI at baseline should have been recommended treatment with AChEIs at the transition to the mild dementia stage. For patients with mild Alzheimer's dementia at baseline who progressed to the moderate stage during the course of the study, both AChEIs and memantine would be suitable treatment options. For patients not taking this medication at the baseline, the study protocol stated that it was not to be initiated during the course of the study, unless medically necessary.
- It is therefore unclear, in relation to both research questions, whether the treatments were discontinued in accordance with the SmPCs in the event of a lack of effectiveness, and whether appropriate therapies were initiated upon progression to the next disease stage.
- Deviations from the donanemab dosage according to the SmPC: The initial dose following protocol amendment a, at 700 mg, remained markedly higher than the initial dose of 350 mg as per the SmPC. Furthermore, investigators were able, in accordance with the study protocol, not only to interrupt and discontinue treatment, but also to continue with reduced doses not specified in the SmPC.
- Lack of information on non-drug therapies: The company does not provide details on the proportion and type of non-drug therapies used during the study.

Subpopulations of the AACI study presented by the company unsuitable

The company presented analyses in Module 4 A for 3 subpopulations: 2 subpopulations relating to the G-BA's research questions, and the combination of both subpopulations, the Module 4 A total population. The company formed subpopulations for the G-BA's research questions, assuming on-label and guideline-compliant prior therapy. To define the subpopulations, the company used the original analysis population from AACI, excluding from this the homozygous ApoE $\epsilon 4$ carriers, who are not part of the approved therapeutic indication for donanemab, and finally excluding patients receiving memantine treatment, as memantine is not approved for the treatment of MCI due to Alzheimer's disease or mild Alzheimer's dementia. The company did not exclude patients with contraindications, particularly those taking anticoagulants. The company then filtered the resulting Module 4 A total population into a 'subpopulation a1' comprising patients not receiving AChEI therapy at screening, hereinafter referred to as the Module 4 A subpopulation without AChEIs. The Module 4 A subpopulation without AChEIs 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, hereinafter referred to as the Module 4 A subpopulation with AChEIs. The Module 4 A subpopulation with AChEIs was presented by the company for research question 2 of the benefit assessment (patients with clinically diagnosed mild dementia due to Alzheimer's disease). The German S3 guideline clearly sets out the approach for diagnosing MCI caused by Alzheimer's disease and mild Alzheimer's dementia, contrary to the company's statement that there is a lack of diagnostic differentiation. In everyday practice, it is possible to distinguish between MCI caused by Alzheimer's disease and mild Alzheimer's dementia on the basis of impairment in daily living skills; however, this is difficult to assess objectively and depends both on patient-individual factors and on the assessing doctor. The identification of subpopulations based solely on the use of a single measurement instrument (e.g. the MMSE) was not considered appropriate, as the company also stated. However, the formation of subpopulations by the company based on the assumption of on-label and guideline-compliant prior therapy was also not appropriate. The Module 4 A subpopulation with AChEIs (presented by the company as patients with mild Alzheimer's dementia) may, in principle, also have included patients with MCI due to Alzheimer's disease who were treated with AChEIs off-label. The size of this group was unclear. However, it could not be assumed that this was a negligible proportion. The inclusion of these patients, who were not treated in accordance with the ACT, is particularly problematic because, in the CLARITY AD study – which was used for the dossier assessment of lecanemab (A25-111) – this patient group was a key factor in the positive, significant effects observed in the overall population. In addition, the Module 4 A subpopulation without AChEIs (presented by the company as patients with MCI) may in principle also have included patients with mild Alzheimer's dementia who had not received

AChEIs for reasons such as availability, lack of effectiveness, side effects, existing contraindications or the patient's own wishes. The size of this group was unclear. However, it could not be assumed that this was a negligible proportion. In particular, it would be problematic if patients were included who, for reasons of availability or due to a lack of review of the treatment/diagnosis at baseline, were not offered treatment with AChEIs – meaning that these patients would be undertreated. In addition to the uncertainties mentioned above, it could not be ruled out that both subpopulations also included patients with moderate Alzheimer's dementia who were not taking memantine. Thus, no suitable data were available for the research questions of this benefit assessment.

Results on added benefit

Since no suitable data were available for the benefit assessment, there is no hint of an added benefit of donanemab in comparison with the ACT; an added benefit is therefore not proven.

Table 3 shows a summary of the probability and extent of the added benefit³ of donanemab.

Table 3: 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
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			

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

The G-BA decides on the added benefit.

I 2 Research question

The aim of this report is to assess the added benefit of donanemab compared with the appropriate comparator therapy (ACT) in adult patients with a clinical diagnosis of mild cognitive impairment (MCI) and mild dementia due to Alzheimer's disease (collectively referred to as early Alzheimer's disease) with confirmed amyloid pathology who are apolipoprotein E ϵ 4 (ApoE ϵ 4) non-carriers or ApoE ϵ 4 heterozygotes.

The research questions presented in Table 4 were defined in accordance with the ACT specified by the Federal Joint Committee (G-BA).

Table 4: 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 ϵ 4 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 interventions as outlined in the Remedies Directive or the catalogue of remedies (occupational therapy, e.g. cognitive training) should be offered in both study arms, where indicated. 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 company followed the G-BA's specification of the ACT for the research questions, divided into MCI and mild dementia, in each case caused by Alzheimer's disease. In Module 4 A, however, the company addressed a 3rd research question in addition to the G-BA's 2 research questions, in which the populations covered by the G-BA's 2 research questions were pooled into a total population, which the company referred to as the 'total target population' and described as 'adult patients with early symptomatic Alzheimer's disease'. The population formed by the company for this 3rd research question is referred to below as the Module 4 A total population. The company cited as the reason for this approach what it saw as a lack of clarity in the definition of the stages of Alzheimer's disease (see also the following section). For this 3rd research question, the company identified 'individualized treatment that takes into account disease progression along the Alzheimer's disease continuum and involves a choice between watchful waiting and the use of acetylcholinesterase inhibitors (AChEIs)' as the ACT. This approach had no bearing on the completeness of the study pool. An assessment

in terms of content can be found in the following section. The assessment of the added benefit was conducted in comparison with the G-BA's ACT presented in Table 4.

The assessment was conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. Randomized controlled trials (RCTs) with a minimum duration of 18 months were used for the derivation of the added benefit. This concurred with the company's inclusion criteria. Further considerations regarding the study duration are set out in Section I 3.2.2.1.

Assessment of the company's reasoning regarding the research questions

In Module 4 A, the company determined what it considered to be a lack of clarity regarding the definition of the stages of Alzheimer's disease and therefore addressed a 3rd research question, in which it combined the populations covered by the G-BA's 2 research questions and referred to them as 'adult patients with early symptomatic Alzheimer's disease'. For this research question, the company defined 'individualized treatment that takes into account disease progression along the Alzheimer's disease continuum and involves a choice between watchful waiting and the use of AChEIs (donepezil or galantamine or rivastigmine)' as the ACT.

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

In its approach of an ACT across the research questions, the company did not take into account the respective approved therapeutic indications for AChEIs, nor the recommendations set out in the guidelines. In addition to patients with MCI due to Alzheimer's disease without

antidementia drugs (addressed in the G-BA's research question 1) and patients with mild Alzheimer's dementia who were treated with AChEIs (addressed in the G-BA's research question 2), the company also considered those patients with MCI due to Alzheimer's disease who were treated off-label with AChEIs, as well as patients with mild Alzheimer's dementia who were not treated. These additional patient populations were not covered by the G-BA's research questions. The relevance of these patient populations to the German health care context is unclear. There are grounds to believe that, particularly in cases where Alzheimer's disease has been diagnosed on the basis of biomarkers, AChEIs are sometimes prescribed as early as the MCI stage [18-21]. It is likely that both the difficult, very individual differentiation from mild Alzheimer's dementia and the patient's (or relatives') desire for early treatment play a role here. In cases of mild Alzheimer's dementia, there are understandable reasons for not treating the condition, such as a lack of effectiveness, side effects, existing contraindications or the patient's own wishes. The size of this group within the German health care system is unclear. In the CLARITY AD study, which was reviewed as part of the dossier assessment for lecanemab in early Alzheimer's disease (A25-111), the proportion of patients not receiving AChEI therapy was approximately one-third of those diagnosed with mild Alzheimer's dementia [22].

In summary, the guidelines clearly set out the diagnostic approach and the recommended treatments. In everyday practice, it is possible to distinguish between MCI caused by Alzheimer's disease and mild Alzheimer's dementia on the basis of impairment in daily living skills; however, this is difficult to assess objectively and depends both on patient-individual factors and on the assessing doctor. The assessment of the added benefit of donanemab was conducted separately for the 2 research questions in Table 4 versus the respective ACT defined by the G-BA.

I 3 Information retrieval and study pool

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

Sources used by the company in the dossier:

- Study list on donanemab (status: 19 September 2025)
- Bibliographical literature search on donanemab (last search on 26 August 2025)
- Search of trial registries / trial results databases for studies on donanemab (last search on 19 August 2025)
- Search on the G-BA website for donanemab (last search on 15 August 2025)

To check the completeness of the study pool:

- Search of trial registries for studies on donanemab (last search on 11 November 2025); for search strategies, see I Appendix A of the full dossier assessment

The search did not identify any additional relevant studies.

I 3.1 Studies included

The study presented in the following table was included in the benefit assessment.

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

Study	Study category			Available sources		
	Study for the marketing authorization of the drug to be assessed (yes/no)	Sponsored study ^a (yes/no)	Third-party study (yes/no)	CSR (yes/no [citation])	Registry entries ^b (yes/no [citation])	Publication and other sources ^c (yes/no [citation])
AACI ^d (TRAILBLAZER-ALZ 2)	Yes	Yes	No	Yes [23]	Yes [24-26]	Yes [27]
a. Study sponsored by the company. b. Citation of the trial registry entries and, if available, of the reports on study design and/or results listed in the trial registries. c. Other sources: documents from the search on the G-BA website and other publicly available sources. d. In the following tables, the study is referred to by this acronym. ACT: appropriate comparator therapy; CSR: clinical study report; G-BA: Federal Joint Committee; RCT: randomized controlled trial						

Concurring with the company, the AACI study was included in the benefit assessment. However, the subpopulations defined by the company in relation to the research questions set out in Table 4 were not appropriate and could not be used for the benefit assessment. The

following sections provide a more detailed description of AACI and explain why the subpopulations formed by the company were not suitable for addressing the research questions of this benefit assessment. Uncertainty remains as to whether it is possible, on the basis of the data collected in the study, to distinguish adequately between patients with MCI and those with mild Alzheimer's dementia.

I 3.2 Study characteristics

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

Table 6: Characteristics of the study included – RCT, direct comparison: donanemab ± AChEI vs. placebo ± AChEI

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes ^a
AACI	RCT, double-blind, parallel	Patients aged ≥ 60 to ≤ 85 years ▪ Gradual and progressive change in memory function for ≥ 6 months ▪ MMSE score of ≥ 20 to ≤ 28 points at screening ▪ Meeting the criteria for the florbetapir F18 PET scan (amyloid pathology) or the flortaucipir F18 PET scan (tau pathology) ▪ With or without prior treatment for Alzheimer's disease	donanemab (N = 860) placebo (N = 876)	Screening: up to 7 weeks Treatment: up to 72 weeks ^b Follow-up: 4 weeks ^c	277 centres in: Australia, Canada, the Czech Republic, Great Britain, Japan, the Netherlands, Poland and the United States 6/2020–4/2023 ^d	Primary: iADRS up to Week 76 ^e Secondary: morbidity, health-related quality of life, AEs
a. Primary outcomes include information without taking into account the relevance for this benefit assessment. Secondary outcomes only include information on relevant available outcomes for this benefit assessment. b. Patients who had amyloid plaque removal at Visit 8 (Week 24) or Visit 15 (Week 52) (either a Centiloid value < 11 in one PET scan or a Centiloid value > 11 and < 25 or both in 2 consecutive PET scans) were switched from donanemab to placebo in a blinded procedure; this was maintained until the end of the study. c. Following the placebo-controlled, double-blind phase, continued treatment as part of a blinded extension phase (Visits 22–41; this phase was implemented via the protocol amendment dated 5 October 2021). If the predefined criteria for the removal of amyloid plaque were met at Week 76, patients in the intervention arm were switched to placebo; otherwise, they continued treatment with donanemab. Patients who received placebo during the double-blind phase were switched to donanemab. The extension phase was followed by a follow-up phase lasting up to 44 weeks. d. Timepoint for the last visit for the placebo-controlled phase of the study (the extension phase of the study has not yet been completed). e. The primary outcome was changed from CDR-SB to iADRS via protocol amendment b (17 February 2021). AChEI: acetylcholinesterase inhibitor; AE: adverse event; CDR-SB: Clinical Dementia Rating-Sum of Boxes; iADRS: Integrated Alzheimer's Disease Rating Scale; MMSE: Mini Mental State Examination; N: number of randomized patients; PET: positron emission tomography; RCT: randomized controlled trial						

Table 7: Characteristics of the interventions – RCT, direct comparison: donanemab ± AChEI vs. placebo ± AChEI

Study	Intervention	Comparison
AACI	donanemab IV every 4 weeks: 700 mg for the first 3 doses^a, followed by 1400 mg Dose modification: ▪ Dose modifications not allowed ▪ Interruption for ARIA events during the titration period^b ▪ Discontinuation for anaphylactic reactions Disallowed prior treatment ▪ Active immunization against amyloid β in any other study ▪ Other passive anti-amyloid immunotherapy within 5 half-lives prior to randomization Allowed concomitant treatment ▪ Continuation of approved medication for the treatment of Alzheimer's disease taken prior to the study, provided it has been taken at a stable dose for ≥ 30 days prior to randomization^c ▪ Continuation of non-medication treatment, such as behavioural management ▪ For the treatment of moderate ARIA-E events: oral or IV steroids; for severe ARIA-E events: inpatient treatment, if necessary with high-dose dexamethasone or an equivalent ▪ Premedication^d or treatment of an infusion-related reaction in accordance with local guidelines Disallowed concomitant treatment ▪ Immunoglobulin G ▪ Other passive anti-amyloid immunotherapies (gantenerumab, lecanemab or aducanumab) ▪ Other effective disease-modifying drugs for the treatment of Alzheimer's disease	placebo IV every 4 weeks
a. Titration was introduced with protocol amendment a of 14 December 2020 (10.5 months after the enrolment of the first patient) due to the occurrence of ARIA-E events. Previously, a dose of 1400 mg was planned from the outset. b. Following the interruption, the titration period could be extended, or the titration dose could continue to be administered for the remainder of the study duration. c. Where medically indicated, the initiation, dose escalation or discontinuation of symptomatic treatment for Alzheimer's disease was permitted. d. Premedication was not planned as standard in the study, but could be administered at the investigator's discretion following an infusion-related reaction. AChEI: acetylcholinesterase inhibitor; ARIA: amyloid related imaging abnormalities; IV: intravenous; RCT: randomized controlled trial		

I 3.2.1 Study description

The AACI study is a randomized, double-blind study on the comparison of donanemab with placebo. The study included patients aged between 60 and 85 years who had experienced a gradual and progressive change in memory function for at least 6 months and had a Mini-Mental State Examination (MMSE) score of at least 20 and no more than 28 points, and who met the positron emission tomography (PET) scan criteria for the presence of amyloid

pathology and tau pathology. The case report form required the patient to be identified as having Alzheimer's disease. There were no further inclusion criteria regarding a diagnosis of MCI due to Alzheimer's disease or early Alzheimer's dementia.

Patients with other neurological disorders of the central nervous system were excluded from the study if these conditions might impair cognition or ability to participate in the study; these included, amongst others, other forms of dementia and Parkinson's disease. Patients with other psychiatric disorders were also excluded from participation if, in the opinion of the investigator, these disorders could interfere with their participation in the study, cognitive testing or the interpretation of the treatment effect; this included, amongst other things, schizophrenia. Patients were also excluded from the study if they had clinically important abnormalities or if the results of their screening magnetic resonance imaging (MRI) suggested another potential aetiology of dementia. Patients were also excluded from the study if they had contraindications to a PET scan or MRI scan, or if their MRI scan revealed evidence of amyloid related imaging abnormalities (ARIA) in the form of an amyloid related imaging abnormality-oedema/effusion (ARIA-E). Patients were also excluded from the study if their MRI scan revealed more than 4 microhaemorrhages or more than 1 area of superficial siderosis. Patients with MRI evidence of any macrohaemorrhage or severe white matter disease were also excluded. Patients with clinically significant liver test abnormalities were also excluded from the study.

A total of 1736 patients were enrolled in AACI, regardless of their ApoE ϵ 4 status, and were randomly assigned to receive donanemab (N = 860) or placebo (N = 876). Allocation was stratified by study centre and tau pathology (intermediate/high).

Concomitant drug treatment for Alzheimer's disease could be continued provided that it had been administered at a stable dose for at least 30 days prior to the start of the study. Where medically indicated, dose modifications could be conducted. Initiation or termination of this drug therapy during the course of the study was also allowed if medically indicated. Non-drug treatment of Alzheimer's disease was permitted, subject to the same restrictions as drug therapy. All patients were required to designate a person who was in regular contact with them (defined as at least 10 hours per week) and who either accompanied them to study visits or could be contacted by telephone.

Treatment with donanemab was not fully in compliance with the summary of product characteristics (SmPC) [28]. In the AACI study, patients received donanemab intravenously every 4 weeks. Initially, a dose of 1400 mg was planned from the start of the study. Titration was introduced following the occurrence of ARIA-E events via protocol amendment a dated 14 December 2020 (10.5 months after the enrolment of the first patient). 43 patients received 1400 mg as an initial dose. In accordance with the protocol amendment, the first 3 doses were each 700 mg. From the 4th dose onwards, the dose was 1400 mg until Week 72 at the latest,

with a blinded switch to placebo if the PET scan at Week 24 or 52 determined a removal of amyloid plaques. The SmPC, however, recommends an initial dose of 350 mg, followed by a dose of 700 mg at the 2nd administration, followed by a dose of 1050 mg at the 3rd. The subsequent doses are to be 1400 mg, as in the AACI study, and, analogous to the study, are to be continued only until the amyloid plaques have been removed (with a maximum permitted treatment duration of 18 months). Following the protocol amendment, the initial dose in the study was therefore 350 mg higher than the dose specified in the SmPC; the 3rd dose, however, was 350 mg lower than the dose specified in the SmPC, meaning that the total planned dose in the AACI study was equivalent to the planned dose specified in the SmPC. Furthermore, the specifications for handling ARIA events in the study deviated from the SmPC. Further details can be found in Section I 3.2.2.3.

The primary outcome of the study was the change in the Integrated Alzheimer's Disease Rating Scale (iADRS) up to Week 76.

I 3.2.2 Limitations of the AACI study

The AACI study was included in the benefit assessment (in accordance with the company), as it included patients relevant to the research questions at hand, notwithstanding the inappropriately defined subpopulations that the company identified. The main limitations are described below; however, they do not call into question the overall relevance of the study.

I 3.2.2.1 Duration of study with limited informative value

According to the European Medicines Agency (EMA) 'Guideline on the clinical investigation of medicines for the treatment of Alzheimer's disease', the study duration in this therapeutic indication should be adapted to the expected progression rate and the expected efficacy of the investigational drug [29]. A study duration of at least 18 months is specified in the early stage of Alzheimer's disease, although longer studies may be necessary in some cases. The US Food and Drug Administration (FDA) guideline for this therapeutic indication, however, recommends a follow-up period of at least 2 years [30]. As early Alzheimer's disease is a condition whose progression spans several years, longer-term studies are necessary, particularly in the case of MCI, in order to adequately investigate further relevant outcomes, such as the loss of independence in everyday life.

In AACI, patients were treated for a maximum of 72 weeks and then followed up for a further 4 weeks, unless they entered the open-label extension phase. As treatment with donanemab is administered every 4 weeks and the last scheduled dose was given in Week 72, the next dose would, according to the SmPC, be administered in Week 76, i.e. at the end of the follow-up period, meaning that the AACI study had a study duration of 76 weeks, or just under 18 months. In this therapeutic indication, 18 months is accepted as the minimum duration. Nevertheless, given that this is a progressive disease which tends to progress rather slowly,

particularly in its early stages, longer follow-up periods would be desirable. The company chose not to present the data from the extension phase of AACI in Module 4 A. This was understandable, as continued treatment with donanemab beyond 18 months is not in accordance with the marketing authorization. Nevertheless, comparative data covering a treatment period for donanemab extending beyond the maximum of 18 months, taking into account appropriate subsequent therapies, would be desirable.

I 3.2.2.2 Uncertainties regarding the population

To be eligible for the AACI study, patients had to meet the inclusion criteria, which required a gradual and progressive change in memory function over a period of at least 6 months, an MMSE score of between 20 and 28 points at screening, and fulfilment of the criteria for PET scans to detect amyloid and tau pathology. However, the presence of Alzheimer's disease in general, or the presence of MCI due to Alzheimer's disease / the presence of mild Alzheimer's dementia in particular, were not specified as inclusion criteria. The case report form simply asked whether the patient had Alzheimer's disease, using the Medical Dictionary for Regulatory Activities (MedDRA) Lowest Level Term (LLT) 'Alzheimer's disease', and the date of diagnosis. Participants also had the option of stating that the diagnosis had been made during the study screening. No information was available as to the criteria on which the diagnosis was based. The disease-related inclusion criteria mentioned above (changes in memory function over at least 6 months and an MMSE score of 20 to 28) did not provide sufficient certainty regarding the clinical diagnosis of Alzheimer's disease or the classification of its severity, meaning that patients outside the therapeutic indication may also have been included. The AACI study therefore did not ensure the exclusion of patients who do not yet meet the criteria for MCI, or of patients with moderate Alzheimer's dementia. In the German health care context, diagnosis according to the S3 guideline is mainly based on a clinical investigation, short cognitive tests (such as MMSE and Montreal Cognitive Assessment [MoCA]) and detailed neuropsychological tests (such as Consortium to Establish a Registry for Alzheimer's Disease [CERAD-plus] and Alzheimer's Disease Assessment Scale-Cognitive subscale [ADAS-Cog]) [5,6]. In addition, other causes of cognitive impairment must be ruled out, for example through blood tests or MRI scans. Distinguishing between MCI and mild Alzheimer's dementia is challenging, as the boundaries between the 2 are blurred and the ability to cope with everyday life is a key distinguishing factor. The assessment depends heavily on individual factors such as education level, age and the extent of abilities prior to the onset of the condition, and on any comorbidities. Research suggests that a neuropsychological assessment, blood tests and MRI scans are almost always carried out [18,21]. In accordance with the requirements for the marketing authorization of donanemab, amyloid pathology will also need to be routinely assessed using a suitable method in the future; however, it is unclear to what extent blood tests might be suitable in the future in

addition to the PET scan used in the marketing authorization study and the lumbar puncture also mentioned as an example in the SmPC [5].

In summary, the AACI study did not require patients to have a clinical diagnosis of MCI or mild Alzheimer's dementia at inclusion, as per the diagnostic approach set out in the guidelines for everyday practice in Germany. This was also discussed by the EMA within the authorization process [27]. Overall, this gave rise to uncertainties regarding the extent to which the study population was representative of patients in the therapeutic indication.

I 3.2.2.3 Uncertainties regarding intervention and concomitant therapy

Lack of information regarding the use of AChEI therapy

In accordance with the inclusion criteria, any existing antidementia treatment for Alzheimer's disease, where administered to a patient, must have been stable for at least 30 days prior to study begin. Patients without antidementia treatment could also participate in the study. Furthermore, antidementia treatment was to be kept stable throughout the study. In both study arms, the increase in dose or discontinuation of existing concomitant antidementia therapy, and the initiation of antidementia therapy in previously untreated patients was permitted if medically necessary.

The company provided details in the dossier regarding patients receiving AChEI treatment at baseline, as well as details regarding any patients who permanently discontinued AChEI treatment, underwent changes to their AChEI treatment or dosage, or commenced AChEI treatment during the course of the study. However, no information was available regarding dosages or the timing of modifications to AChEI therapy. However, this information would be necessary in order to check whether the drugs of the ACT were also administered in compliance with the SmPC. According to the relevant SmPCs, AChEIs should be titrated to the maximum tolerated dose over a defined period, taking into account clinical response and tolerability [13-15]. Clinical response should also be monitored as treatment continues. Discontinuation of treatment should be considered if no therapeutic effect is evident. Fundamentally, treatment with AChEIs should be initiated and monitored by a doctor with experience in the diagnosis and treatment of Alzheimer's disease. There were no signs that AChEIs were not used in accordance with the SmPC in the AACI study; however, the relevant data were not available for verification.

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

According to the SmPC, donanemab is approved for the treatment of MCI and mild dementia, both caused by Alzheimer's disease. If the disease progresses to the moderate stage, treatment must be discontinued before the end of the maximum treatment duration of 18 months. Discontinuation of treatment with donanemab in case of progression to the

moderate stage was not planned for in the study. If continued treatment with donanemab were to occur in the moderate stage, this would constitute off-label use. The study did not include an overall assessment by the doctors regarding progression or the transition to moderate Alzheimer's dementia. The proportion of patients with progression to moderate Alzheimer's dementia and thus an indication for discontinuation was therefore unclear.

Regular assessment of cognitive functioning and clinical symptoms is recommended for both donanemab and AChEIs [13-15,28,31]. Among other things, this review is intended to help determine whether treatment should be discontinued if there is a lack of clinical effectiveness. An overall assessment by the physicians regarding a lack of effectiveness, with corresponding requirements to discontinue donanemab or AChEIs, was not allowed for. With the exception of on-label discontinuation once the amyloid plaques had been removed (or switching to placebo in the study), discontinuation of donanemab was only envisaged in the event of certain side effects. The study protocol stipulated that existing AChEI treatment should be continued as far as possible without change. Modifications to the therapy were to be avoided, but could be made if medically necessary. The company provided limited information on modifications to AChEI treatment. Reasons for treatment modifications were, however, not provided. It was therefore unclear whether the AChEIs were discontinued due to a lack of therapeutic effectiveness or whether treatment with another drug was possibly initiated.

AChEIs are approved for the treatment of mild and moderate Alzheimer's dementia [13-15]. According to the guidelines, patients with MCI at baseline should have been recommended treatment with AChEIs at the transition to the mild dementia stage [5]. For patients with mild Alzheimer's dementia at baseline who progressed to the moderate stage during the course of the study, both AChEIs and memantine would be suitable treatment options. For patients not taking this medication at the baseline, the study protocol stated that it was not to be initiated during the course of the study, unless medically necessary. It is therefore unclear, in relation to both research questions, whether the treatments were discontinued in accordance with the SmPCs in the event of a lack of effectiveness, and whether appropriate therapies were initiated upon progression to the next disease stage.

Deviations from the donanemab dosage according to the SmPC

Deviations from the SmPC in the AACI study regarding the dosing regimen for the first 3 doses were already outlined in Section I 3.2.1. Only 5% of the donanemab patients received an initial dose of 1400 mg. The titration regimen, which had been amended with the protocol amendment, also did not comply with the SmPC. At 700 mg, the initial dose remained markedly higher than the initial dose of 350 mg as per the SmPC. That the dosage at baseline was too high may reduce the certainty of conclusions, especially in time-to-event analyses, regarding the results of the morbidity and side effects outcomes.

Other deviations in the administration of donanemab in AACI versus the SmPC relate to treatment interruptions or treatment discontinuation, in each case as a result of ARIA; this includes ARIA-E and the amyloid related imaging abnormality-microhaemorrhages and haemosiderin deposits (ARIA-H). In the AACI study, in accordance with the study protocol with amendments a and b (amendment a dated 14 December 2020 and amendment b dated 17 February 2021), in the event of ARIA occurring within the first 3 doses of donanemab, the investigator could temporarily interrupt treatment, continue with the current dose without increasing it, or continue the dosing schedule unchanged. Treatment discontinuation due to ARIA was decided at the discretion of the investigator based on the severity of the clinical and radiological findings; a manual was available to assist with this decision, although it was not included in the company's dossier. In Module 4 A, the company provided specifications in Figure 4-5 on how to handle ARIA events. It remained unclear whether this figure was taken from the manual mentioned above, when these specifications came into effect, and to what extent they were mandatory. By comparing the SmPC and the information regarding the management of ARIA as set out in the study protocol it could be seen that in the study, treatment interruptions and discontinuations were largely at the discretion of the investigator, whereas the SmPC provides detailed specifications based on radiological criteria for assessing severity. Furthermore, investigators were able, in accordance with the study protocol, not only to interrupt and discontinue treatment, but also to continue with reduced doses not specified in the SmPC. The clinical study report showed that there were patients who continued to receive donanemab at a dose of 700 mg even after the titration phase. However, the number of patients receiving a dose of 700 mg following the titration phase, which is off-label, was not available.

MRI scan prior to the 3rd infusion not scheduled

In the study, scheduled MRI scans were carried out at Week 4 (with results available before the 2nd infusion), at Week 12 (with results before the 4th infusion), and at Weeks 24, 52 and 76, as well as in the event of treatment discontinuation before Week 76. This differs from the SmPC, which also specifies an MRI prior to the 3rd infusion (in the 2nd month of treatment). As the study did not include an MRI scan prior to the 3rd infusion, ARIA may have been undetected, or may only have been detected later in the course of treatment. The need to interrupt or discontinue treatment may also not have been noticed or only noticed at a later stage. Furthermore, symptoms such as headaches or dizziness that occurred between the 2nd and 4th infusions were potentially not recorded as symptomatic ARIA.

Lack of information on non-drug therapies

In the study, an existing non-drug antidementia treatment for Alzheimer's disease was allowed, provided that this had been implemented consistently for at least 30 days prior to the baseline. In both study arms, a modification or discontinuation of an existing non-drug

antidementia treatment, and the initiation of a non-drug antidementia treatment in previously untreated patients, was permitted if medically necessary.

According to the current S3 guideline, non-drug treatments such as cognitive training, cognitive stimulation or physical exercise are recommended for both of the relevant patient populations [5]. It should also be noted that with regard to the ACT, non-drug measures as outlined in the German Remedies Directive or the catalogue of remedies (occupational therapy, e.g. cognitive training) were to be offered and documented in both study arms. As already described, since antidementia treatments such as AChEIs or memantine are not approved or recommended for patients with MCI, non-drug treatments are of particular importance for these patients. Patients with mild Alzheimer's dementia might, however, also benefit from these. Non-drug treatments were permitted during the study, but were not offered as part of the study. It was assumed that they were used, provided they were medically indicated and available. The company did not provide details on the proportion and type of non-drug therapies used during the study. This gave rise to uncertainties regarding the implementation of the ACT and the transferability to the German health care context.

I 3.2.3 Subpopulations of the AACI study presented by the company unsuitable

As already described in Chapter I 2, the company presented analyses in Module 4 A for 3 subpopulations: 2 subpopulations relating to the G-BA's research questions, and the combination of both subpopulations, the Module 4 A total population. According to the company, there are no internationally established, specific criteria for the diagnostic differentiation between MCI and mild dementia. The company described the transitions between the disease stages as fluid and the disease itself as a continuum. It said that the classification of stages also depends on many patient-individual factors, such as personal abilities, habits, living circumstances and coping mechanisms, as well as information provided by relatives and, ultimately, the doctor'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, 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 the company's view, the scores obtained from individual instruments as part of a clinical study – whether from the screening phase or at the baseline – are also unsuitable for distinguishing between disease stages, as they are difficult to interpret without knowledge of the longitudinal course and are additionally influenced by any prior treatment with antidementia drugs. It stated that the treatment situation is therefore the best possible indicator of the disease stage. For these reasons, the company formed subpopulations for the G-BA's research questions, assuming on-label and guideline-compliant prior therapy. To define the subpopulations, the company used the original analysis population from AACI, excluding from this the homozygous ApoE ϵ 4 carriers, who are not part of the approved therapeutic indication for donanemab, and finally excluding patients receiving memantine

treatment, as memantine is not approved for the treatment of MCI due to Alzheimer's disease or mild Alzheimer's dementia. The company did not exclude patients with contraindications, particularly those taking anticoagulants. The company then filtered the resulting Module 4 A total population into a 'subpopulation a1' comprising patients not receiving AChEI therapy at screening, hereinafter referred to as the Module 4 A subpopulation without AChEIs. The Module 4 A subpopulation without AChEIs 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, hereinafter referred to as the Module 4 A subpopulation with AChEIs. The Module 4 A subpopulation with AChEIs was presented by the company for research question 2 of the benefit assessment (patients with clinically diagnosed mild dementia due to Alzheimer's disease). As already outlined in Chapter I 2, the S3 guideline clearly sets out the approach for diagnosing MCI caused by Alzheimer's disease and mild Alzheimer's dementia. In everyday practice, it is possible to distinguish between MCI caused by Alzheimer's disease and mild Alzheimer's dementia on the basis of impairment in daily living skills, even though this distinction is difficult to assess objectively and depends both on patient-individual factors and on the assessing doctor. The identification of subpopulations based solely on the use of a single measurement instrument (e.g. the MMSE) was not considered appropriate, as the company also stated. However, the formation of subpopulations by the company based on the assumption of on-label and guideline-compliant prior therapy was also not appropriate. The Module 4 A subpopulation with AChEIs (presented by the company as patients with mild Alzheimer's dementia) may, in principle, also have included patients with MCI due to Alzheimer's disease who were treated with AChEIs off-label. The size of this group was unclear. However, it could not be assumed that this was a negligible proportion. As already described, there are grounds to believe that, particularly in cases where Alzheimer's disease has been diagnosed on the basis of biomarkers, AChEIs are sometimes prescribed as early as the MCI stage [18-21]. The inclusion of these patients was also particularly problematic because, in the CLARITY AD study, this patient group was the main reason for the positive, significant effects in the total population [22]. In addition, the Module 4 A subpopulation without AChEIs (presented by the company as patients with MCI) may in principle also have included patients with mild Alzheimer's dementia who had not received AChEIs for reasons such as availability, lack of effectiveness, side effects, existing contraindications or the patient's own wishes. The size of this group was unclear. However, it could not be assumed that this was a negligible proportion. In the CLARITY AD study, the proportion of untreated patients was around 1/3 of patients diagnosed with mild Alzheimer's dementia [22]. In particular, it would be problematic if patients were included who, for reasons of availability or due to a lack of review of the treatment/diagnosis at baseline, were not offered treatment with AChEIs – meaning that these patients would be undertreated. In addition to the uncertainties mentioned above, it could not be ruled out that both

subpopulations also included patients with moderate Alzheimer's dementia who were not taking memantine (see also Section I 3.2.2.2 regarding uncertainties relating to diagnosis in the AACI study). Thus, no suitable data were available for the research questions of this benefit assessment. The subpopulations presented by the company in relation to the G-BA's research questions are discussed in the following sections with regard to their patient characteristics.

I 3.2.3.1 Characteristics of the subpopulations presented by the company

Research question 1 considers the patient population of adult patients with clinically diagnosed MCI due to Alzheimer's disease who are ApoE ε4 non-carriers or heterozygotes. For this purpose, the company presented the Module 4 A subpopulation without AChEIs. Research question 2 considers the patient population of adult patients with clinically diagnosed mild Alzheimer's dementia who are ApoE ε4 non-carriers or heterozygotes. For this purpose, the company presented the Module 4 A subpopulation with AChEIs.

The patient characteristics of these populations are presented below.

Patient characteristics

Table 8 shows the characteristics of the patients in the included study for the Module 4 A subpopulation without AChEIs presented by the company.

Table 8: Characteristics of the study population as well as study/treatment discontinuation – RCT, direct comparison: donanemab vs. placebo (Module 4 A subpopulation without AChEIs) (multipage table)

Study Characteristic Category	donanemab N^a = 284	placebo N^a = 270
AACI		
Age [years], mean (SD)	74 (6)	73 (6)
Sex [F/M], %	63/37	60/40
Family origin, n (%)		
White	260 (92)	245 (91)
Black or African American	8 (3)	7 (3)
Asian	15 (5)	18 (7)
Other	1 (< 1)	0 (0)
Time since symptom onset [years], mean (SD)	3.6 (2.7)	3.4 (2.2)
Time since diagnosis of Alzheimer's disease [years], mean (SD)	0.9 (1.4)	1.0 (1.7)
MMSE score, mean (SD)	23.7 (3.8)	22.9 (3.9)
MMSE score, n (%)		
27-30	77 (27 ^b)	53 (20 ^b)
20-26	206 (73 ^b)	216 (80 ^b)
ADAS-Cog13, mean (SD)	25.5 (8.9)	26.7 (8.9)
ADCS-iADL, mean (SD)	49.6 (7.5)	49.6 (7.5)
iADRS, mean (SD)	109.1 (14.0)	107.9 (13.8)
CDR-SB, mean (SD)	3.4 (2.1)	3.4 (1.9)
CDR-GS, n (%)		
0	1 (< 1)	2 (< 1)
0.5	205 (72)	187 (69)
1	67 (24)	72 (27)
2	7 (2)	4 (1)
ApoE ε4 carrier status, n (%)		
Heterozygotes	186 (65)	182 (67)
Non-carriers	98 (35)	88 (33)
Amyloid PET imaging at baseline [Centiloids], mean (SD)	104.4 (35.8)	100.3 (34.7)
Number of microhaemorrhages at baseline, n (%)		
0	243 (86)	233 (86)
1	33 (12)	26 (10)
2	5 (2)	3 (1)
3	1 (< 1)	6 (2)
4	2 (< 1)	2 (< 1)

Table 8: Characteristics of the study population as well as study/treatment discontinuation – RCT, direct comparison: donanemab vs. placebo (Module 4 A subpopulation without AChEIs) (multipage table)

Study Characteristic Category	donanemab N ^a = 284	placebo N ^a = 270
Any contraindications at baseline, n (%) ^c	19 (7)	21 (8)
Superficial siderosis or vasogenic oedema at baseline, n (%)	3 (1)	7 (3)
Use of anticoagulants at baseline, n (%)	16 (6)	13 (5)
Uncontrolled blood pressure at baseline, n (%)	0 (0)	1 (< 1)
Initiation of any AChEI, n (%)	27 (10)	36 (13)
Treatment discontinuation, n (%) ^d	74 (26)	49 (18)
Study discontinuation, n (%) ^e	68 (24)	49 (18)
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 (10% vs. 3%), patient request (9% vs. 11%). In addition, 3 (1%) vs. 1 (< 1%) of the randomized patients never started treatment. Furthermore, 71% vs. 81% of the patients completed treatment as planned. e. Common reasons for study discontinuation in the intervention arm vs. control arm were the following (percentages based on randomized patients): AEs (4% vs. 2%), patient request (13% vs. 11%). 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; 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; iADRS: Integrated Alzheimer's Disease Rating Scale; M: male; MMSE: Mini Mental State Examination; n: number of patients in the category; N: number of randomized patients; PET: positron emission tomography; RCT: randomized controlled trial; SD: standard deviation		

The characteristics of patients in the Module 4 A subpopulation without AChEIs were largely comparable across the treatment arms. The mean age of patients was 74 years and 73 years, and the majority were female and of white family origin. On average, symptoms had begun 3.6 and 3.4 years previously, and the diagnosis had been made 0.9/1 year earlier. With regard to their findings from disease-specific measurement instruments such as the MMSE, the ADAS-Cog13, the Alzheimer's Disease Cooperative Study-instrumental Activities of Daily Living subscale (ADCS-iADL), the iADRS, the Clinical Dementia Rating-Sum of Boxes (CDR-SB) and the Clinical Dementia Rating-Global Score (CDR-GS), the treatment arms were largely comparable. With regard to ApoE ε4 carrier status, 65% and 67% were heterozygous carriers. In both arms, 86% of patients had no microhaemorrhages at baseline. At baseline, 7% and 8% of patients, respectively, had contraindications to the administration of donanemab, according to the

SmPC. AChEI treatment was initiated in 10% and 13% of patients during the course of the study.

Treatment was discontinued more frequently in the intervention arm than in the comparator arm (26% versus 18%). The most common reason for treatment discontinuation in the intervention group was adverse events (AEs); in the comparator arm the reason was patient request. 24% and 18% of patients, respectively, discontinued the study.

Table 9 shows the characteristics of patients in the included study for the subpopulation presented by the company for research question 2 (Module 4 A subpopulation with AChEIs).

Table 9: Characteristics of the study population as well as study/treatment discontinuation – RCT, direct comparison: donanemab + AChEI vs. placebo + AChEI (Module 4 A subpopulation with AChEIs) (multipage table)

Study Characteristic Category	donanemab + AChEI N^a = 277	placebo + AChEI N^a = 291
AACI		
Age [years], mean (SD)	73 (6)	73 (6)
Sex [F/M], %	56/44	57/43
Family origin, n (%)		
White	242 (87)	262 (90)
Black or African American	3 (1)	5 (2)
Asian	30 (11)	23 (8)
Other	2 (< 1)	1 (< 1)
Time since symptom onset [years], mean (SD)	4.1 (2.4)	3.7 (2.0)
Time since diagnosis of Alzheimer's disease [years], mean (SD)	1.6 (1.6)	1.4 (1.5)
MMSE, mean (SD)	21.9 (3.6)	22.0 (3.7)
MMSE score, n (%)		
27-30	28 (10 ^b)	45 (15 ^b)
20-26	249 (90 ^b)	246 (85 ^b)
ADAS-Cog13, mean (SD)	30.2 (8.4)	29.6 (8.8)
ADCS-iADL, mean (SD)	47.4 (7.7)	47.8 (7.5)
iADRS, mean (SD)	102.2 (13.5)	103.2 (13.4)
CDR-SB, mean (SD)	4.2 (2.0)	4.0 (1.8)
CDR-GS, n (%)		
0	1 (< 1)	0 (0)
0.5	150 (54)	181 (62)
1	112 (40)	106 (36)
2	10 (4)	4 (1)
ApoE ε4 carrier status, n (%)		
ApoE ε4 heterozygotes	173 (62)	182 (63)
ApoE ε4 non-carriers	104 (38)	109 (37)
Amyloid PET imaging at baseline [Centiloids], mean (SD)	102.6 (33.5)	102.5 (34.4)
Number of microhaemorrhages at baseline, n (%)		
0	250 (90)	252 (87)
1	21 (8)	25 (9)
2	3 (1)	11 (4)
3	2 (< 1)	2 (< 1)
4	1 (< 1)	1 (< 1)

Table 9: Characteristics of the study population as well as study/treatment discontinuation – RCT, direct comparison: donanemab + AChEI vs. placebo + AChEI (Module 4 A subpopulation with AChEIs) (multipage table)

Study Characteristic Category	donanemab + AChEI N ^a = 277	placebo + AChEI N ^a = 291
Any contraindications at baseline, n (%) ^c	21 (8)	26 (9)
Superficial siderosis or vasogenic oedema at baseline, n (%)	4 (1)	7 (2)
Use of anticoagulants at baseline, n (%)	14 (5)	19 (7)
Uncontrolled blood pressure at baseline, n (%)	3 (1)	0 (0)
Use of any AChEI at baseline, n (%)	274 (100)	291 (100)
donepezil	225 (82)	233 (80)
galantamine	24 (9)	24 (8)
rivastigmine	25 (9)	36 (12)
Permanent discontinuation of all AChEI therapy during the double-blind phase, n (%)	6 (2)	12 (4)
Modification to AChEI treatment or dosage during the double-blind phase, n (%)	23 (8)	33 (11)
Treatment discontinuation, n (%) ^d	80 (29)	57 (20)
Study discontinuation, n (%) ^e	76 (27)	56 (19)
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 (10% vs. 2%), patient request (11% vs. 11%). In addition, 3 (1%) vs. 0 of the randomized patients never started treatment. Furthermore, 70% vs. 80% of the patients completed treatment as planned. e. Common reasons for study discontinuation in the intervention arm vs. control arm were the following (percentages based on randomized patients): AEs (7% vs. 2%), patient request (13% vs. 11%). 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; 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; iADRS: Integrated Alzheimer's Disease Rating Scale; M: male; MMSE: Mini Mental State Examination; n: number of patients in the category; N: number of randomized patients; PET: positron emission tomography; RCT: randomized controlled trial; SD: standard deviation		

The characteristics of patients in the Module 4 A subpopulation with AChEIs were largely comparable across the treatment arms. The average age of patients was 73 years, and the majority were female and of white family origin. On average, symptoms had begun 4.1 and 3.7 years previously, and the diagnosis had been made 1.6/1.4 years earlier. With regard to the results obtained from disease-specific measurement instruments, such as the MMSE, ADAS-Cog13, ADCS-iADL, iADRS, CDR-SB and CDR-GS, the treatment arms were largely

comparable. With regard to ApoE ϵ 4 carrier status, 62% and 63% were heterozygous carriers. 90% and 87% of patients, respectively, had no microhaemorrhages at baseline. At baseline, 8% and 9% of patients, respectively, had contraindications to the administration of donanemab, according to the SmPC. In both arms, treatment with AChEIs was predominantly with donepezil. In 2% and 4% of patients, respectively, AChEI treatment was permanently discontinued during the study, whilst dose modifications to AChEI treatment were made in 8% and 11% of patients.

Treatment was discontinued more frequently in the intervention arm than in the comparator arm (29% versus 20%). The most common reason for treatment discontinuation was patient request. 27% and 19% of patients, respectively, discontinued the study.

Table 10 presents a comparison of disease-related patient characteristics for the populations from Module 4 A.

Table 10: Comparison of disease-related patient characteristics for the populations from Module 4 A

Study Characteristic Category	Module 4 A total population		Module 4 A subpopulation without AChEIs		Module 4 A subpopulation with AChEIs	
	donanemab ± AChEI N ^a = 561	placebo + AChEI N ^a = 561	donanemab N ^a = 284	placebo N ^a = 270	donanemab + AChEI N ^a = 277	placebo + AChEI N ^a = 291
AACI						
Time since symptom onset [years], mean (SD)	3.9 (2.6)	3.6 (2.1)	3.6 (2.7)	3.4 (2.2)	4.1 (2.4)	3.7 (2.0)
Time since diagnosis of Alzheimer's disease [years], mean (SD)	1.3 (1.6)	1.2 (1.6)	0.9 (1.4)	1.0 (1.7)	1.6 (1.6)	1.4 (1.5)
MMSE, mean (SD)	22.8 (3.8)	22.4 (3.8)	23.7 (3.8)	22.9 (3.9)	21.9 (3.6)	22.0 (3.7)
MMSE score, n (%)						
27-30	ND	ND	77 (27 ^b)	53 (20 ^b)	28 (10 ^b)	45 (15 ^b)
20-26	ND	ND	206 (73 ^b)	216 (80 ^b)	249 (90 ^b)	246 (85 ^b)
CDR-SB, mean (SD)	3.8 (2.1)	3.7 (1.9)	3.4 (2.1)	3.4 (1.9)	4.2 (2.0)	4.0 (1.8)
CDR-GS, n (%)						
0	2 (< 1)	2 (< 1)	1 (< 1)	2 (< 1)	1 (< 1)	0 (0)
0.5	355 (63)	368 (66)	205 (72)	187 (69)	150 (54)	181 (62)
1	179 (32)	178 (32)	67 (24)	72 (27)	112 (40)	106 (36)
2	17 (3)	8 (1)	7 (2)	4 (1)	10 (4)	4 (1)
ADAS-Cog13, mean (SD)	27.8 (8.9)	28.2 (9.0)	25.5 (8.9)	26.7 (8.9)	30.2 (8.4)	29.6 (8.8)
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. 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						

A comparison of disease-related patient characteristics for the populations from Module 4 A showed that the subpopulations of the company did not differ markedly in terms of various scales or the duration of the disease. As already discussed in Chapter I 2, the average duration of the MCI stage is 3 to 7 years [7]. Beyond the issue of a lack of relevant group differences between the subpopulations presented by the company regarding the average time since diagnosis, the average time since diagnosis appeared to be particularly short in the Module 4 A subpopulation with AChEIs (presented by the company as patients with early symptomatic Alzheimer's disease). Although the timing of diagnosis depends on the health care context and individual patient characteristics such as age, ApoE genotype, sex and the extent of tau pathology [7], the extent of the discrepancy with the aforementioned data on disease progression was striking. The lack of distinguishability between subpopulations of the company in terms of disease severity was also evident from the baseline values in disease-specific measurement instruments. In the Module 4 A subpopulation without AChEIs, the mean CDR-SB scores at baseline were 3.4 points in both the intervention arm and the comparator arm. In the Module 4 A subpopulation with AChEIs, the mean CDR-SB scores at baseline were 4.2 points in the intervention arm and 4.0 points in the comparator arm. These values all fall within the range reported in the literature for MCI [32,33]. Although, as already discussed, a diagnosis of MCI due to Alzheimer's disease or mild Alzheimer's dementia is not made on the basis of individual measurement instruments, and the available data only allowed conclusions to be drawn regarding group means, the subpopulations presented by the company differed only marginally in the mean CDR-SB. This was also evident in the CDR-GS and the other measurement instruments, so that it could be concluded that, assuming on-label prior treatment in accordance with guidelines, the division of the populations by the company did not result in the formation of subpopulations with clearly distinguishable disease severity.

No data were available from study populations that represent the populations relevant to the research questions addressed in this benefit assessment.

I 3.2.4 Transferability of the study results to the German health care context

The company stated that only limited information was available to assess the transferability of the study results to the German health care context. It continued that for this reason, subgroup analyses for the region characteristic were considered to assess the transferability of the study results, which did not result in any effect modifications relevant to the conclusion. Furthermore, the company said that patients for AACI were recruited in the United States, Canada, Australia, the Netherlands, Poland, Great Britain, the Czech Republic and Japan, all of which are member countries of the Organisation for Economic Co-operation and Development (OECD). It continued that these countries not only have a high per capita income by global standards but also possess efficient health care systems, and have been working towards joint reporting on selected quality indicators for health care since 2003. The company stated that

according to IQWiG, this implies that guidelines from these countries are transferable to the German health care system, which is why the transferability of study results was also assumed. Overall, the company therefore generally assumed that the findings of the AACI study have transferability to the German health care context. There were no signs to the contrary, it added.

The company did not provide any further information on the transferability of the study results to the German health care context. For the transferability of the study results to the German health care context, see also Section I 3.2.2.

I 4 Results on added benefit

No suitable data were available from the company's dossier for the assessment of donanemab in comparison with the ACT in adult patients with clinically diagnosed MCI or mild dementia due to Alzheimer's disease (collectively referred to as early Alzheimer's disease) with confirmed amyloid pathology who are ApoE ε4 non-carriers or heterozygotes. There is no hint of an added benefit of donanemab in comparison with the ACT. An added benefit is therefore not proven.

I 4.1 Probability and extent of added benefit – summary

The result of the assessment of the added benefit of donanemab in comparison with the ACT is summarized in Table 11.

Table 11: 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
a. Presented is the respective ACT specified by the G-BA. b. Non-drug interventions as outlined in the Remedies Directive or the catalogue of remedies (occupational therapy, e.g. cognitive training) should be offered in both study arms, where indicated. 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 assessment described above deviates from that of the company, which derived an indication of a considerable added benefit for both patient groups. The G-BA decides on the added benefit.

I 5 References for English extract

Please see full dossier assessment for full reference list.

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