24 July 2025
EMA/298973/2025
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Kisunla

International non-proprietary name: donanemab

Procedure No. EMEA/H/C/006024/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

AChEI	acetylcholinesterase inhibitor
AD	Alzheimer's disease
ADAS-Cog13	Alzheimer's Disease Assessment Scale – 13-item Cognitive subscale
ADCS-ADL	Alzheimer's Disease Cooperative Study – Activities of Daily Living subscale
ADCS-iADL subscale	Alzheimer's Disease Cooperative Study – instrumental Activities of Daily Living
AE	adverse event
APOE-ε4	allele subtype 4 of the gene coding for apolipoprotein class E
ARIA	amyloid related imaging abnormalities
ARIA-E	amyloid-related imaging abnormalities–oedema/effusions (also known as vasogenic oedema)
BMI	body mass index
CDR-G	Clinical Dementia Rating Scale – Global Score
CDR-SB	Clinical Dementia Rating Scale – Sum of Boxes
CI	confidence interval
CL	Centiloid
COVID-19	coronavirus disease 2019
CrI	credible interval
CSR	clinical study report
DPM	disease progression model
DPR	disease progression ratio
EMA	European Medicines Agency
HR	hazard ratio
iADRS	integrated Alzheimer's Disease Rating Scale
IRR	infusion-related reaction
IV	intravenous
LS	least squares
MCI	mild cognitive impairment
MMRM	mixed model for repeated measures
MMSE	Mini-Mental State Examination
NCS2	natural cubic spline with 2 degrees of freedom
NCS3	natural cubic spline with 3 degrees of freedom
PD	pharmacodynamic(s)

PET	positron emission tomography
PK	pharmacokinetic
PMRM	progression model for repeat measures
P-tau217	tau phosphorylated at threonine 217; also known as phospho-tau 217
SAP	statistical analysis plan
SE	standard error
SS	safety set
SUVr	standardised uptake value ratio
SUVrCLAA	standardised uptake value ratio cerebellum longitudinal Avid analysis

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Eli Lilly Nederland B.V. submitted on 24 July 2023 an application for marketing authorisation to the European Medicines Agency (EMA) for Kisunla, through the centralised procedure falling within Article 3(1) and point 1 of Annex of Regulation (EC) No 726/2004

The applicant applied for the following indication: Donanemab is indicated for the treatment of adult patients with a clinical diagnosis of mild cognitive impairment and mild dementia due to Alzheimer's disease (Early symptomatic Alzheimer's disease) who are apolipoprotein E ε4 (ApoE ε4) non-carriers with confirmed amyloid pathology (see section 4.4).

1.2. Legal basis, dossier content

The legal basis for this application refers to:

Article 8(3) of Directive 2001/83/EC - complete and independent application

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

1.3. Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) CW/1/2015 on the granting of a class waiver.

1.4. Information relating to orphan market exclusivity

1.4.1. Similarity

Pursuant to Article 8 of Regulation (EC) No 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

1.4.2. Accelerated assessment

The applicant requested accelerated assessment in accordance with Article 14 (9) of Regulation (EC) No 726/2004.

1.4.3. New active substance status

The applicant requested the active substance donanemab contained in the above medicinal product to be considered as a new active substance, as the applicant claims that it is not a constituent of a medicinal product previously authorised within the European Union.

1.5. Scientific advice

The applicant received the following scientific advice on the development relevant for the indication subject to the present application:

Date	Reference	SAWP co-ordinators
14 October 2021	EMA/SA/0000054826	*Andre Elferink, Elena Wolff-Holz*
15 September 2022	EMA/SA/0000093898	*Ewa Balkowiec Iskra and Elina Ronnemaa*

The applicant received scientific advice on the development of donanemab to slow disease progression in patients with early symptomatic Alzheimer's disease from the CHMP on 14 October 2021 (EMA/SA/0000054826). The scientific advice pertained to the following clinical and non-clinical aspects:

- Non-clinical: the weight of evidence is adequate to support the low risk of carcinogenicity with donanemab; assessment of developmental and reproductive Risk
- Clinical: agreement that Study AACG could support a conditional approval of donanemab for the treatment of early symptomatic AD; that study AACI can confirm the positive benefit-risk profile that has been established in Study AACG for the treatment of early symptomatic AD; that iADRS as the primary outcome measure (analysed using Bayesian DPM); interim analyses for early efficacy or futility.
- Agreement that the estimated size of the safety database to support an initial regulatory approval of donanemab in the following scenarios for the indication of early symptomatic AD is acceptable: Conditional MAA based on results of Study AACG (and Studies AACC and AACD); MAA submission based on results of Study AACG (and Studies AACC and AACD), and interim results of Study AACI; MAA submission based on results of Study AACG (and Studies AACC and AACD), and Study AACI complete results.
- The biomarkers for diagnostic testing for the presence of tau by PET scan is necessary; that diagnostic testing for presence of tau is not limited to PET scan.

The scientific advice (EMA/SA/0000093898) pertained to the following clinical aspects:

- Neuropathological requirements for treatment initiation, classification of in vitro diagnostic tests used to confirm eligibility for treatment and for treatment monitoring; treatment duration; patient preference survey

1.6. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Peter Mol Co-Rapporteur: Grzegorz Cessak

The appointed CHMP co-rapporteur had no such prominent role in scientific advice relevant for the indication subject to the present application.

The application was received by the EMA on	24 July 2023
The procedure started on	17 August 2023

The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	6 November 2023
The CHMP Co-Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	21 November 2023
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	20 November 2023
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	14 December 2023
The applicant submitted the responses to the CHMP consolidated List of Questions on	22 February 2024
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	2 April 2024
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	11 April 2024
The CHMP agreed on a list of outstanding issues in writing and/or in an oral explanation to be sent to the applicant on	25 April 2024
The applicant submitted the responses to the CHMP List of Outstanding Issues on	8 November 2024
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	27 November 2024
The outstanding issues were addressed by the applicant during an oral explanation before the CHMP during the meeting on	11 December 2024
The CHMP agreed on a 2nd list of outstanding issues in writing and/or in an oral explanation to be sent to the applicant on	12 December 2024
The applicant submitted the responses to the 2nd CHMP List of Outstanding Issues on	27 January 2025
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	12 February 2025
The outstanding issues were addressed by the applicant during an oral explanation before the CHMP during the meeting on	26 February 2025
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a negative opinion for granting a marketing authorisation to Kisunla on	27 March 2025
Furthermore, the CHMP adopted a report on New Active Substance (NAS) status of the active substance contained in the medicinal product	27 March 2025

1.7. Steps taken for the re-examination procedure

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Daniela Philadelphy Co-Rapporteur: Jan Mueller-Berghaus

The applicant submitted written notice to the EMA, to request a re-examination of Kisunla CHMP opinion of 27 March 2025., on	10 April 2025
The applicant submitted the detailed grounds for the re-examination on	30 May 2025
The re-examination procedure started on	31 May 2025
The CHMP Rapporteur's re-examination assessment report was circulated to all CHMP members on	02 July 2025
The CHMP Co-Rapporteur's assessment report was circulated to all CHMP and PRAC members on	02 July 2025
The detailed grounds for re-examination were presented by the applicant during an oral explanation before the CHMP on	21 July 2025
The CHMP, in the light of the scientific data available and the scientific discussion within the Committee, re-examined its initial opinion and, in its final opinion, concluded that the application satisfied the criteria for authorisation and recommended the granting of the marketing authorisation on	24 July 2025

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

Alzheimer's disease (AD) is an age-related neurodegenerative disorder characterised by an inexorable progressive decline in cognitive and functional abilities, ultimately with a fatal outcome. AD (the most common cause of dementia) is an irreversible, progressive neurodegenerative disorder that affects language, memory, and thinking skills and ultimately the ability to carry out daily activities (Hoy 2023). The amyloid cascade hypothesis of AD posits that the production and deposition of Aβ plaques in the brain is an early and necessary event in the pathogenesis of AD (Hardy and Higgins 1992; Hardy and Selkoe 2002).

The claimed indication is: "Donanemab is indicated to slow disease progression in symptomatic adult patients with Alzheimer's disease (AD) with evidence of amyloid beta pathology and a clinical diagnosis of either mild cognitive impairment due to AD or mild AD dementia". During the course of the MAA, the indication was restricted to exclude APOE-E4 homozygous patients, and further restricted to APOE-E4 non-carriers only. The now sought indication is "Donanemab is indicated for the treatment of adult patients with a clinical diagnosis of mild cognitive impairment and mild AD dementia due to Alzheimer's disease (Early symptomatic Alzheimer's disease) who are apolipoprotein E ε4 (ApoE ε4) non-carriers with confirmed amyloid pathology (see section 4.4)."

2.1.2. Epidemiology and risk factors

Currently more than 55 million people have dementia worldwide, over 60% of whom live in low- and middle-income countries. Every year, there are nearly 10 million new cases identified (WHO 2023). The number of people living with dementia in the European Union (EU27) is estimated to be approximately 7.8 million and in European countries represented by Alzheimer Europe members, approximately 9.8 million (Alzheimer Europe 2023).

The greatest risk factors for AD include older age, genetics (especially the e4 form of the APOE gene), and a family history of AD (Alzheimer's Association 2022; Alzheimer Europe 2019). Less than 5% of all AD cases exhibit an autosomal dominant inheritance pattern (Wu et al. 2012). The remaining 95% are the non-dominantly inherited type known as sporadic AD, in which the APOE ε4 acts as the strongest genetic risk factor (Alzheimer's Association 2022). Many factors that increase the risk of cardiovascular disease are also associated with a higher risk of sporadic AD (Roberts and Knopman 2013; Alzheimer's Association 2022). These factors include active smoking and diabetes (Anstey et al. 2007; Durazzo et al. 2014; Lee et al. 2018). High serum cholesterol, hypertension, and obesity, particularly in midlife, have been shown to be associated with increased AD risk (Anstey et al. 2011; Meng et al. 2014; Anstey et al. 2017; Lennon et al. 2019). Other factors such as physical activity, healthy diet, more years of education, and being socially and mentally active are associated with a reduced AD risk (Chen et al. 2016; Rege et al. 2017; Alzheimer's Association 2021).

2.1.3. Aetiology and pathogenesis

In the amyloid cascade of AD, the production and deposition of Aβ plaques in the brain is an early and necessary event in the pathogenesis of AD (Hardy and Higgins 1992, Hardy and Selkoe 2002). Clinical support for this cascade comes from the demonstration that parenchymal amyloid levels are elevated before the appearance of symptoms of AD (Jack et al. 2013), there are genetic variants of AD that result in the overproduction of brain Aβ (Fleisher et al. 2015), and there are genetic variants that afford protection against amyloid production (Jonsson et al. 2012).

2.1.4. Clinical presentation, diagnosis and stages

During the progression of AD from brain changes that are unnoticeable to the affected person to brain changes resulting in problems with memory and eventually physical disability, there are 3 broad phases: pre-clinical AD, Mild Cognitive Impairment (MCI) due to AD, and AD dementia (Alzheimer's Association 2021; Alzheimer Europe 2019). Depending on the degree to which symptoms interfere with one's ability to carry out daily tasks, the AD dementia phase is further broken down into mild, moderate, and severe stages (Alzheimer's Association 2021; Alzheimer Europe 2019). The indicated population with mild AD dementia may be able to function independently in many daily tasks but is likely to require assistance with some activities to maximise independence and remain safe (Alzheimer's Association 2021; Alzheimer Europe 2019).

MCI, which does not interfere with individuals' ability to carry out daily tasks (Alzheimer's Association 2021; Alzheimer Europe 2019), can be subdivided into aMCI (memory impaired) and non-aMCI (other domains affected, memory preserved; Roberts and Knopman 2013). Both types can be categorised further to single-domain and multi-domain subtypes according to the number of cognitive domains involved. aMCI is associated with a considerable risk to further conversion to AD dementia, while non-aMCI presentation may frequently progress to non-AD dementias (Roberts and Knopman 2013). Individuals diagnosed with MCI may remain stable, return to being neurologically intact, or progress to dementia (Petersen et al. 2018). In the Rotterdam study, MCI was associated with an increased risk of

dementia (HR = 3.98, 95% CI: 2.97, 5.33) and AD (HR = 4.03, 95% CI: 2.92, 5.56) (de Bruijn et al. 2014). A systematic review and meta-analysis estimated that individuals with MCI were 3 times more likely to be diagnosed with AD dementia 2 to 5 years later as compared to the age-matched controls without MCI (Petersen et al. 2018). The annual conversion rate from aMCI to AD dementia was estimated between 5.6% and 16.5% per PY among community-based and clinic-based cohorts of patients (Ward et al. 2013).

Decline in memory has been considered the predominant and earliest symptom of AD, followed by impairments of other cognitive domains such as language, executive function, praxis, and complex visual processing, though heterogeneity in the presentation and course of cognitive impairments have been identified (Dubois et al. 2010). Behavioural and psychological symptoms have also been recognised as a key feature of AD dementia (Robert et al. 2005; Bature et al. 2017). A systematic review and meta-analysis of 48 studies across Europe, Asia, and the US showed that the most frequent behavioural or psychological symptom among individuals with AD was apathy with a pooled prevalence of 49%, followed by depression (42%), aggression (40%), anxiety (39%), and sleep disorder (39%) (Zhao et al. 2016). Another review found that the prevalence of any behavioural or psychological symptoms was between 35% and 85% among individuals with MCI who had a mean age ranging from 65.2 to 80.6 years across studies in different settings (Monastero et al. 2009). Patients who eventually progress to the severe stage of AD dementia need help with daily tasks and are likely to require around-the-clock care. Therefore, dementia is a disease that impacts patients, their families, and ultimately the healthcare system. Severe dementia frequently causes complications, including immobility, swallowing disorders, and malnutrition, that significantly increase the risk of serious acute conditions such as pneumonia (Brucki et al. 2022).

Individuals with MCI or AD dementia are at increased risk of mortality. Across studies, the HR of all-cause mortality among individuals with MCI ranged from 1.5 to 2.0 when compared to that among individuals without cognitive impairment (Guehne et al. 2007; Wilson et al. 2009; Vassilaki et al. 2015). The estimated HR relating AD dementia to all-cause mortality ranged from 1.4 to 3.1 in population-based studies (Ganguli et al. 2005; Wilson et al. 2009; Lönnroos et al. 2013; James et al. 2014). The median survival time was estimated as 8.3 years for individuals diagnosed as having AD at age 65 years and 3.4 years for individuals diagnosed as having AD at age 90 years (Brookmeyer et al. 2002). A European study of death data in 28 countries estimated that the overall age-standardised mortality rate of AD increased from 28.2 to 45.2 per 100,000 people during 1994 to 2013 (Niu et al. 2017b). It also found that the estimated AD mortality rate was highest in Finland (278.9 per 100,000) and lowest in Malta and Latvia (less than 5 per 100,000) in 2013 (Niu et al. 2017b). In a Dutch cross-sectional analysis of the population-based Rotterdam study, MCI was associated with an increased risk of mortality: HR = 1.54, 95% CI: 1.28, 1.85 (de Bruijn et al. 2014). In Europe, data from 1994 to 2003 Eurostat and WHO databases were analysed and mortality from AD has risen in the EU throughout the study period. Most of the countries showed upward trends, with the sharpest increases in Slovakia, Lithuania, and Romania. Statistically significant increases of 4.7% and 6.0% in mortality rates in men and women, respectively, in the whole EU were recorded (Niu et al. 2017b).

2.1.5. Management

The approved AD therapies, such as donepezil, rivastigmine, galantamine, and memantine, have only modest and transitory effects on symptoms.

No new medicines for AD have been introduced in the EU for over 15 years. Approved treatment options for patients with mild to moderately severe AD are the cholinesterase inhibitors (donepezil, rivastigmine, and galantamine) and, for patients with moderate to severe AD, the N-methyl-D-

aspartate antagonist; memantine. These agents provide symptomatic benefit with a limited duration of effect due to progression of the disease.

Several previous clinical studies with other anti-Aβ monoclonal antibodies (bapineuzumab, solanezumab, crenezumab and gantenerumab,) did not to meet their clinical endpoints. Recently, the MAA for aducanumab was withdrawn since the CHMP reached a negative opinion because the pharmacodynamic effect (i.e., reduction of brain amyloid load) was not translated into clinical benefit. In addition, β-site amyloid precursor protein cleaving enzyme (BACE) inhibitors were stopped due to safety findings. Lecanemab is the first amyloid-targeting therapy approved in the EU (CHMP confirmed positive opinion in February 2025). Lecanemab targets amyloid protofibrils in the brain and may slow the progression of the disease.

Hence, there is still an unmet medical need for an effective and safe treatment in AD in an ageing European population in which the prevalence of AD increases.

2.2. About the product

Donanemab belongs to an emerging class of amyloid-targeting therapies whose mechanisms of action are intended to modify the underlying pathology and slow cognitive and functional decline in patients with AD. Donanemab is an immunoglobulin gamma 1 (IgG1) mAb directed against insoluble, modified, N-terminal truncated form of amyloid beta (N3pG Aβ) present only in brain amyloid plaques (Bridel et al. 2017). Donanemab binds to the deposited amyloid plaque and aids its removal through microglial-mediated phagocytosis (DeMattos et al. 2012).

Donanemab is intended for use in patients with early symptomatic AD, including those with MCI or mild dementia stage of AD. Proposed labelling included in this MAA submission recommends the dosing regimen: donanemab 700 mg IV administered every 4 weeks for the first 3 doses, followed by 1400 mg IV every 4 weeks thereafter.

In contrast with other amyloid-targeting drugs that are in development, donanemab binds specifically to amyloid plaques. Importantly, because of the ability of donanemab to significantly lower amyloid plaque levels, there is no or minimal target for treatment to bind to once the mature plaques have been removed and no further expected benefit. Thus, the clinical programme was designed to allow patients to complete a course of treatment based on observed amyloid imaging results.

2.3. Type of application and aspects on development

The CHMP did not agree to the applicant's request for an accelerated assessment as the product was not considered to be of major public health interest. This was based on the strength of evidence for efficacy and on safety concerns.

2.4. Quality aspects

2.4.1. Introduction

Kisunla finished product (FP) is presented as concentrate for solution for infusion containing 350 mg in 20 ml (17.5 mg/ml) of donanemab as active substance (AS). Other ingredients are: citric acid, polysorbate 80, sodium citrate, sucrose and water for injections.

The product is available in a type I clear glass, 20 ml, single dose vial with a chlorobutyl elastomer stopper and an aluminium seal with a polypropylene cap.

Kisunla is supplied in pack sizes of 1 vial and multipacks containing 2 (2 packs of 1) vials.

2.4.2. Active substance

2.4.2.1. General information

Donanemab (INN) is a humanized IgG1 monoclonal antibody produced by recombinant expression in Chinese hamster ovary (CHO) cells.

It is composed of two identical immunoglobulin kappa light chains (LC) and two identical immunoglobulin gamma heavy chains (HC). Each HC contains a single N-linked glycosylation site at Asn295. The N-linked glycosylation structure is predominantly a fucosylated, complex biantennary glycan with 0 galactose residues on either arm (G0F). Donanemab consists of two identical LC polypeptides of relative molecular weight 23,915 Da and two identical HC polypeptides of relative molecular weight 48,657 Da, yielding a molecular weight of 145,111 Da for the protein backbone of the donanemab molecule.

Donanemab is directed against insoluble, modified, N-terminal truncated form of amyloid beta (N3pG Aβ) present only in brain amyloid plaques. It recognizes the Aβ(p3-42) peptide, a pyroglutamate form of the Aβ peptide which is aggregated in the amyloid plaques in the brain of Alzheimer's patients. Donanemab specifically targets the amyloid plaques in the brain and activates microglial cells via its Fc. Donanemab binds to deposited amyloid plaque and induces removal through microglial-mediated phagocytosis.

2.4.2.2. Manufacture, characterisation and process controls

Manufacturers

The active substance is manufactured by Eli Lilly Kinsale Limited, Dunderrow Kinsale, Co. Cork, P17 NY71 Ireland.

The responsibilities of all sites involved in the manufacture and quality control testing of the active substance have been specified. All sites are compliant with EU GMP.

Description of the manufacturing process and process control

Flow diagrams depicting the manufacturing process and accompanying narratives for each unit step describing the step purpose and its respective controls have been provided.

The manufacturing process of the active substance consists of an upstream and a downstream process.

The upstream manufacture of each batch of donanemab begins with the thawing of a single vial of the WCB, that is sequentially scaled-up in flasks and seed bioreactors. The culture is harvested, clarified, and then transferred for downstream processing.

The purified donanemab (bulk drug substance) is filtered, dispensed into the container closure system, and stored.

Critical controls and non-critical operating ranges are specified in tabular overviews. In-process hold times, reprocessing storage and transfer conditions are specified. For the chromatography columns, regeneration, storage and cleaning is also described.

The manufacturing process description is sufficiently detailed and adequately supported by process evaluation/validation studies.

Control of materials

Cell banks

A comprehensive description of the development genetics as well as schematic overviews and narratives of the development of the cell banks have been provided. The description of the process is sufficiently detailed.

Raw materials of animal origin were used in the generation of the production cell line. A safety assessment has been provided and does not give rise to any concerns.

One MCB and two WCB were developed from the pre-master research cell bank and MCB, respectively. The process is described in sufficient detail. No animal component-containing raw materials were used in the production of the MCB and WCBs.

The MCB and WCBs were tested in accordance with ICH Q5A(R1). No adventitious agents were detected apart from C-type retrovirus-like particles, which is acceptable for CHO cells.

A protocol is provided for the manufacturing of replacement WCBs should such a need occur. Replacement WCBs will be tested in the same manner as the current WCBs.

Genetic stability testing of the MCB and cells at Limit of In Vitro Cell Age (LIVCA) evaluated gene copy number, insertions and deletions, integration patterns and cDNA sequence of the donanemab LC and HC coding genes, in compliance with ICH Q5B.

Raw materials

A tabulated overview of the raw materials used in the manufacture of the AS is presented for each unit operation. In addition, cell culture media and feed solutions are described in detail. The buffer and other solutions are described detailing the ingredients and their concentration targets. None of the raw materials used in the active substance manufacturing process are of animal or human source.

Raw materials are divided into compendial and non-compendial and testing parameters for the non-compendial raw materials are provided. Material qualification includes an evaluation of the supplier's material specification including certificate of analysis (CoA) where available, supplier audits and regulatory compliance.

Filters and membranes used in the manufacturing process are described for their respective unit operations. Potential leachables were evaluated, no potential leachables of toxicological concern were identified.

Control of critical steps and intermediates

The applicant has provided the definitions for critical process parameters, critical in process controls, in process specifications, operational process parameters and in process controls. A brief description of the procedure in case of departures of the control strategy is provided.

In process specifications are in place for microbial and virus safety. Brief method descriptions and summaries of the method validation/qualification are provided.

The information provided on critical process parameters (CPPs), critical in-process controls (CIPCs) and non-critical controls is in line with S.2.2.

An overview of the in-process hold times of intermediates is provided. The proposed storage temperatures and durations are supported by laboratory scale studies.

Process validation and evaluation

In general, the manufacturing process is appropriately validated.

Results do not give rise to any concerns. All process validation batches met the release acceptance criteria and results confirm that the manufacturing process reproducibly produces donanemab AS of consistent quality.

Impurity clearance was evaluated. Levels were sufficiently reduced. A brief statement was provided regarding the nitrosamine risk evaluation that was performed and no risk of presence of nitrosamines was identified. Upon request, the applicant provided a risk evaluation for both the AS and FP manufacturing processes covering all possible sources of nitrosamines, mentioned in the current version of "Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products". The risk assessment sufficiently supported the view that the donanemab manufacturing process does not have a significant risk of the formation of nitrosamines.

Laboratory scale studies have been performed to evaluate the stability of the process intermediates during the claimed in-process hold times. Laboratory scale vessels used in intermediate hold-time studies have been described and it was justified that they are representative for commercial vessels.

Lifetime studies have been performed for the chromatography resins. Results give no reason for concern.

Laboratory scale reprocessing studies were performed. No impact was observed. The protocols provided for reprocessing are acceptable.

AS shipping studies were performed to validate the transport of AS to FP formulation sites. Shipment is by air and by ground/sea. This shipping study design can be accepted and results in general do not give rise to any concerns.

The information provided is adequate and sufficient.

Manufacturing process development

An overview of the manufacturing processes have been presented, including batch numbers, batch use, batch sizes, and process changes applied during the manufacturing development.

The general approach for the comparability studies is acceptable.

The approach to defining robust process control and analytical testing strategies for the donanemab commercial drug substance and donanemab commercial drug product manufacturing processes was based on science and risk-based decisions that leveraged product and process understanding. ICH Q8(R2), Q9, Q10, and Q11 guidance documents were used in the development of the donanemab process control and analytical testing strategies. The quality target product profile (QTPP) summarises the donanemab finished product characteristics that are required in order to achieve the desired quality, safety, and efficacy of the product. Elements of the QTPP include, but are not limited to, dosage form, administration route, product stability, and product CQAs. The overall risk assessments for the donanemab commercial active substance and donanemab finished product process control and analytical testing strategies have been sufficiently described.

Overall, the control strategy is considered state-of-the-art, and was based on an in depth understanding of each process step, supported by well-coordinated development activities. This part of the dossier is found acceptable.

Characterisation

An overview of the structural elucidation and characterisation of donanemab has been provided including detailed descriptions of the structural, physicochemical, and biological characterisation.

The primary structure of donanemab was elucidated using various techniques.

Several orthogonal biophysical techniques were used to characterise the higher order structure of donanemab.

Overall, the performed characterisation studies are considered relevant and cover a wide variety of physicochemical and biological characterisation studies.

Impurities

The product-related and process-related impurities in donanemab were identified and characterised. The information provided in this section is sufficient.

2.4.2.3. Specification

The active substance release and shelf-life specifications include control of identity, quantity, potency, purity/impurities, bacterial endotoxins and other general tests.

The selection of tests to be included in the active substance specification is considered acceptable.

To define acceptance criteria for the active substance release tests, the applicant considered the clinical experience of donanemab, the potential risk of the CQA to the patient, and the stability of the active substance and the finished product. This approach is acceptable.

Analytical procedures

Method descriptions of the in-house analytical methods are provided in tabular form and include general information, operating parameters, preparations used, system suitability criteria, and data analysis and reportable results. Methods are appropriately validated.

Batch analysis

An overview of the active substance batches, that were used to manufacture finished product batches and the clinical trial in which they have been used, was provided.

All results met their acceptance criteria. Supportive batch analysis results are provided for additional batches, that were not manufactured at the intended commercial scale.

Reference standards

A two-tiered reference standard (RS) programme for donanemab has been implemented, which includes a primary reference standard (PRS) and a secondary/working reference standard (WRS).

Analytical procedures used for the characterisation of the donanemab PRS and WRS were the same as those used for release and stability testing of donanemab, along with the characterisation assays.-The reference standard control strategy is properly described.

Container closure

Donanemab bulk drug substance is filled into an irradiated polymeric container, sealed with a polymeric closure.

The extractable and leachable studies performed do not give rise to any questions since all detected leachables are below the limit of 10 µg/dose, as specified in ICH M7.

The proposed container closure system is justified for storing the active substance regarding stability, integrity and compatibility of the medicinal product.

2.4.2.4. Stability

The stability results provided support the proposed shelf-life. The containers used for the AS stability studies are representative of the commercial closure container system used for storage of the AS.

Supporting results from stress testing have been provided and demonstrate that the AS is light sensitive.

In conclusion and based on the stability data provided the claimed shelf-life for the active substance at the recommended storage conditions is considered acceptable.

2.4.3. Finished Medicinal Product

2.4.3.1. Description of the product and pharmaceutical development

Kisunla finished product is presented as a concentrate for solution for infusion containing 350 mg in 20 ml (17.5 mg/ml) of donanemab as active substance. Other ingredients are: citric acid, polysorbate 80, sodium citrate, sucrose and water for injections.

Kisunla is supplied as a sterile, non-pyrogenic, preservative-free solution in a 20 mL glass Type I, single dose vial closed with an elastomeric stopper and an aluminium seal with a polypropylene cap.

There are no overages present in a donanemab finished product vial.

All excipients comply with the Ph. Eur. The finished product does not contain any novel excipients or any excipients of human or animal origin. The general properties of the active substance important for *the* pharmaceutical form are sufficiently described.

Pharmaceutical development

A combination of specification testing, biochemical, and biophysical characterisation testing was utilized to assess the comparability of donanemab finished product batches

Comparability has been confirmed by available batch release data and stability data and support the changes made to the finished product during development.

The primary container closure system (CCS) is a 20-mL clear Type-I glass tubing vial with a chlorobutyl elastomer stopper that is further sealed in place with an aluminium seal consisting of a two-piece, polypropylene/aluminium, flip-top design. The container closure system components comply

with the current version of the relevant compendia; the suitability of the product contacting components of the container closure system has been established.

The extensive extractables and leachables studies included worst-case conditions and confirm suitability of the CCS for donanemab finished product. Shipping studies performed support the shipping conditions. The sterilisation and depyrogenisation processes of the container closure components have been described in sufficient detail.

2.4.3.2. Manufacture of the product and process controls

Manufacturers

The addresses and responsibilities of all sites involved in the manufacturing, packaging, labelling, and control of the finished product are provided. All sites are compliant with EU GMP.

Manufacturing process

The finished product manufacturing process is standard for a monoclonal antibody and consists of buffer excipient solution compounding, finished product formulation compounding, sterile filtration, filling, stoppering and sealing, visual inspection and packaging and labelling.

Operating ranges for process parameters and acceptance criteria for controls are provided for the parameters/controls that have been determined to be critical to ensure that the CQAs are met. Ranges are also provided for non-critical process parameters and controls. The hold times and conditions were validated.

The provided description and flow of the finished product manufacturing is sufficient to understand the process and the process is sufficiently documented.

Donanemab finished product is stored at 2°C to 8°C protected from light. The finished product is typically shipped at 2°C to 8°C.

Process controls

A risk assessment was conducted on the donanemab finished product formulation compounding operation to evaluate the impact of process variables on finished product CQAs.

The control strategy is sufficiently justified based on the process characterisation studies. The criticality of Process parameters and Process Controls has been sufficiently described. The various quality attributes have been evaluated and the selection of CQAs has been appropriately justified. Ranges are also provided for a subset of non-critical process parameters and controls (for example, Operational Process Parameters (OPP) and In-Process Controls (IPC)).

Process validation

For process validation, active substance, excipients, critical consumables and container/closure components batches were varied across the three donanemab PPQ finished product batches as available.

Process validation was performed at the proposed commercial finished product manufacturing site.

The provided data support the notion that the process is validated and under control. Batch variability will continue to be monitored as part of ongoing process verification. The hold times were deliberately

exceeded to confirm that the hold times were appropriate to ensure endotoxin and microbial safety and do not impact product quality. In-process sampling consisted of routine and expanded sampling to confirm product uniformity across the filling operations.

The validation data provided show that the production is consistent, controlled and robust.

2.4.3.3. Product specification

The finished product release and shelf-life specifications all parameters expected for a monoclonal antibody, including control of identity, quantity, potency, purity/impurities, charge heterogeneity, sterility and other general tests.

All excipients comply with the applicable compendial standards and testing is performed accordingly.

The proposed acceptance criteria are based upon consideration of the clinical experience of donanemab, the potential risk of the CQA to the patient, and the stability of the finished product.

For the CQAs with a potential to directly impact the patient, including quantity, potency, aggregation, charge heterogeneity and fragmentation, the proposed end of shelf-life acceptance criteria are based upon the donanemab clinical experience as well as a risk assessment of the potential patient impact.

Overall, the proposed finished product release and shelf-life specifications are adequately justified and considered acceptable.

The information provided on elemental impurities is in line with ICH Q3D. The applicant's conclusion that no additional control measures are required is acceptable.

A risk evaluation for both the AS and FP manufacturing processes covering all possible sources of nitrosamines, mentioned in the current version of "Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products", was provided. The risk assessment sufficiently supported the view that the donanemab manufacturing process does not have a significant risk of the formation of nitrosamines.

Analytical methods

The compendial analytical procedures that are used to control finished product were verified in accordance with the relevant Ph. Eur. Monographs. The product complies with Ph. Eur. 2031 and is tested according to Ph. Eur. 2.9.20 (taking into account Ph. Eur. 5.17.2). The validation of the non-compendial assays has been discussed in the AS part. The information provided is sufficient.

Batch analysis

The batch data provided demonstrate that the manufacturing process can consistently produce batches meeting the release specifications and therefore is able to deliver Kisunla finished product with a consistent and predefined quality profile.

Reference standards

The same reference standards are used for testing of the finished product as for active substance (see active substance section).

Container closure

Donanemab finished product is packaged in a 20 mL clear, Type I glass tubing vial with a chlorobutyl elastomer stopper that is further sealed in place with a two piece flip-top aluminium seal. The

container closure system components comply with the current version of Ph. Eur. 3.2.1 (vial) and Ph. Eur. 3.2.9 (stoppers). The secondary packaging has been described.

Extensive extractables and leachables studies were performed and included worst-case conditions (e.g., inverted vials). The results confirm the safety of the vial CCS for donanemab. A donanemab vial laboratory shipping study was performed and sufficiently supports the shipping conditions.

The sterilisation and depyrogenisation processes of the container closure components are described in sufficient detail.

In summary, the proposed container closure system is appropriate for storing Kisunla finished product regarding stability, integrity and compatibility of the medicinal product.

2.4.3.4. Stability of the product

A shelf-life of 24 months when stored at 2°C to 8°C is claimed for the finished product.

Stability studies were conducted in accordance with relevant ICH guidelines. Primary stability studies were performed for 24 months at the long-term storage condition (2°C to 8°C) on several batches of finished product manufactured at the commercial manufacturing site using the commercial manufacturing process using active substance from the commercial process. The containers used for the FP stability studies are representative of the commercial closure container system used for storage of the FP.

In addition, accelerated stability studies were performed on the same batches. Container closure integrity has also been demonstrated for 24 months. These stability studies support the proposed 24 months shelf-life. The accelerated stability conditions showed trends in several parameters confirming that the shelf-life parameters are stability indicating.

The compatibility studies (including microbial challenge studies) support the proposed in-use stability including 72h of diluted product at 2°C to 8°C, or for up to 12h at room temperature (up to 25°C), in-use stability data has been presented to confirm proposed in-use shelf-life and storage conditions. Photosensitivity was demonstrated. The secondary packaging materials provide protection from light.

In conclusion and based on the stability studies results, the claimed shelf-life of 24 months for the finished product when stored at 2°C to 8°C is acceptable. Furthermore, the unopened vial may be stored unrefrigerated for up to 3 days at room temperature (up to 25°C).

For the diluted solution, the prepared dosing solution should be used immediately. If not used immediately, the donanemab dosing solution should be kept in a refrigerator (2°C to 8°C) for up to 72 hours or for up to 12 hours at room temperature (up to 25°C) assuming dilution has taken place using aseptic techniques. Storage times include the duration of infusion.

2.4.3.5. Adventitious agents

In line with ICH Q5A, Q5D, and Q6B and FDA Points to consider for biologicals/monoclonal antibodies, the adventitious agent safety strategy consists of the following features:

1. Controls of sourcing, documentation, and testing of raw materials used in cell line generation and in the production of donanemab.

2. Screen testing of the MCB, WCB, and unprocessed bulk (UPB) for adventitious agents (bacteria, fungi, mycoplasma, and viruses).

3. Screen testing of cells beyond the LIVCA to ensure that no new viruses are induced or introduced by the cell culture process conditions.

4. Spike-recovery studies using four model viruses to demonstrate that the downstream purification process can effectively clear viruses with broad ranges of biochemical and biophysical properties.

Safety assessment of animal-sourced materials

Animal-sourced materials were used in the cell line generation. A safety assessment has been provided and certification, sourcing, and treatment of the materials are sufficient to minimise the risk of adventitious agents being introduced into the manufacturing process.

None of the raw materials used in the active substance and finished product manufacturing process are animal sourced.

Testing

The MCB and WCB have been tested for adventitious agents, as well as cells beyond LIVCA and the unprocessed bulk.

Virus removal steps

Several orthogonal dedicated virus removal/inactivation unit operations are included in the donanemab purification process.

Virus validation studies

In accordance with the ICH Q5A guideline, individual unit operations were evaluated for virus removal/inactivation using model viruses to determine the overall virus clearance capacity of the donanemab purification process and sufficient removal was demonstrated.

Acceptable information has been provided to ensure safety of the product with regards to adventitious agents.

2.4.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The stability results support the proposed shelf life for active substance and finished product. Acceptable information has been provided to ensure safety of the product with regards to adventitious agents.

2.4.5. Conclusions on the chemical, pharmaceutical and biological aspects

The overall quality of Kisunla is considered acceptable when used in accordance with the conditions defined in the SmPC. The different aspects of the chemical, pharmaceutical and biological documentation comply with existing guidelines. In conclusion, based on the review of the data provided, the marketing authorisation application for Kisunla is considered approvable from the quality point of view.

2.4.6. Recommendation(s) for future quality development

N/A

2.5. Non-clinical aspects

2.5.1. Introduction

Donanemab is a human immunoglobulin gamma 1 (IgG1) monoclonal antibody (mAb) targeting an N-terminal pyroglutamate (N3pE) Aβ epitope present in brain amyloid beta (Aβ) plaques. The originally applied indication for donanemab was to slow the progression of Alzheimer's disease (AD) when initiated in patients with early symptomatic AD with underlying amyloid and tau pathologies. During the course of the MAA, this was restricted to APOE-E4 non-carriers only. The murine anti-Aβ monoclonal antibody from which donanemab was derived is known as mE8. The antibodies were developed to specifically target a neo-epitope present only in deposited plaque, the Aβp3-X. The anti-Aβp3-X antibodies were developed to target the removal of pre-existing deposited amyloid plaque from brain through the phagocytosis as mechanism of action.

2.5.2. Pharmacology

Primary pharmacodynamic studies

The target of donanemab is the Aβp3-42 peptide (also referred to as N3pG or N3pE). Notably, in the name N3pG, the "G" refers to glutamate, and not to glycine. The N3pE peptide is a pyroglutamate form of the Aβ peptide in which the first two amino acid residues are absent (truncated) and the third amino acid residue is modified as pyroglutamate. The modification can occur spontaneously or by the action of glutaminyl cyclase. After immunizing mice with this modified form of Aβ, Fabs were identified to be specific for N3pE Aβ. A high-affinity antibody (mE8) was optimized to be specific for N3pE Aβ.

N3pE is a modified form of Aβ expected to be only found in deposited Aβ plaques but not in soluble Aβ. Antibodies targeting forms of Aβ only present in plaque were hypothesized to be more effective compared to other Aβ mAbs as they do not become saturated with soluble Aβ.

By expressing this antibody as isotype that promotes effector function (mouse isotype IgG2A, mE8c), significant clearance of N3pE through microglia-mediated antibody-dependent cellular phagocytosis (ADCP) is expected. As such, donanemab antibody-mediated clearance of N3pE involving the engagement of Fcγ receptors to perform ADCP is a plausible mode of action.

The affinity of mE8c and the humanized antibody donanemab were characterized in vitro by using surface plasmon resonance (SPR). The specific epitope was characterized using a set of derivatives of pE3-16 peptide, the N-terminal 14 residues of N3pE Aβ. The murine parental antibody mE8c exhibited a binding affinity (K_D) for Aβp3-42 (N3pE-42) of <0.2 nM. Donanemab retains an epitope specificity with a binding affinity of 0.82 nM. N3pE mAbs do not recognize the natural N terminus of the Aβ peptide (starting at aa1),and require a modified pyro-Glu N-terminus (aa3) for high affinity binding to a set of derivatives of pE3-16 peptide. In clinical studies, concentrations of donanemab in CSF were around 2 nM. Neither of these antibodies bind to human Aβ1-40 peptide at concentrations up to 1 μM, suggesting that donanemab does not bind to (soluble), unmodified Aβ in vitro and providing indirect evidence that N3pE Aβ is present only in brain amyloid plaques.

Ex vivo studies were performed to investigate whether the anti-N3pE antibodies, mE8, or mE8c, would facilitate microglial phagocytosis of AD plaque. These anti-N3pE antibodies significantly facilitated the clearance of deposited plaque compared to treatment with microglia alone in sections from an Aβ containing AD brain. The mE8c antibody facilitated more Aβ clearance compared to mE8, suggesting that Fc function is important in clearing donanemab bound Aβ. The 3D6 antibody led to a similar

clearance as anti-N3pE antibodies. These data suggest that a potential mE8c-mediated clearance mechanism involves microglia-mediated phagocytosis.

The ability of murine surrogate and humanized anti-N3pE antibodies to engage the target was evaluated ex vivo using brain sections derived from an aged PDAPP transgenic mouse and an AD patient. In vivo target engagement was also evaluated following administration of antibodies to aged PDAPP mice. Ex vivo, mE8 labelled only a subset of Aβ deposits compared to 3D6. Human N3pE antibodies were also shown to bind to the deposited Aβ in AD brain. In vivo, both mE8 and human N3pE antibodies were described to engage deposited target in vivo throughout the hippocampus and cortical regions, while 3D6 was described to induce limited target engagement along the hippocampal fissure. These results would suggest that both murine and human anti-N3pG antibodies are able to pass the blood-brain-barrier (BBB) in mice and are able to engage with the target.

The ability of mE8c to reduce Aβ1-42 in the brain of 23-24 months old PDAPP mice was evaluated in a 3 month study. Treatment with either mE8 or mE8c (12.5 mg/kg) resulted in significant plaque lowering in the hippocampus, compared to the negative control IgG2a. The m3D6 antibody lacked plaque lowering efficacy. ME8c tended to being more efficacious than mE8, suggesting that Fc function is important in clearing donanemab bound Aβ. ME8c also significantly cleared hippocampal Aβ1-42 that had deposited prior to treatment. Analyses of plaque load in cortical lysates yielded similar outcomes with the exception that only mE8c significantly decreased Aβ1-42 deposition. In a six month study, efficacy of mE8c was evaluated in 16 month old PDAPP female mice, where animals received either 1.5, 4 or 12.5 mg/kg per week. The Aβ plaque load in the cortex and hippocampus was dose-dependently lower in animals treated with mE8c compared to IgG control, though not lower compared to the plaque levels prior to treatment.

Further, an inhibitory maximum effective level (E_{max}) PK/PD model was developed to relate mE8c plasma concentrations to Aβ1-42 levels in the hippocampus and cortex of PDAPP mice following 6 months of weekly dosing. The E_{max} showed near maximal responses in mice dosed with 12.5 mg/kg, suggesting that the administration of mE8c at doses greater than 12.5 mg/kg would not be expected to produce a greater pharmacological effect. However, it should be noted that higher doses were not tested to confirm this hypothesis and a study report with the underlying data was not presented. Furthermore, only one plasma concentration time point, i.e., at termination, was used and there seems to be much variation. Therefore, the relevance of this model is considered limited.

Increases in plasma Aβ1-40 was described to be an in vivo surrogate for antibody binding to physiological levels of endogenous Aβ1-40. There was no significant increase in plasma Aβ1-40 for mE8c and donanemab, suggesting that these antibodies will not bind soluble Aβ1-40.

The ability of mE8c to prevent plaque deposition was evaluated in a prevention study in 5.5-month old PDAPP mice treated for 7 months. At study initiation, these 5.5-month old mice lacked deposited Aβ1-42 while levels of hippocampal Aβ1-42 rose significantly over the course of the study. ME8c treatment resulted in a non-significant decrease in hippocampal Aβ1-42 as compared to the IgG-treated control mice, in contrast to 3D6 treatment. These results indicate that mE8c does not significantly prevent Aβ1-42 deposition in young PDAPP transgenic mice. This is in line with lower levels of the target, modified N3pE Aβ, in mice at 12 months compared to 23 months of age (DeMattos et al. 2012).

Overall, the proof of concept has been sufficiently demonstrated. Donanemab binds to N3pE containing amyloid beta plaques, which were demonstrated to be reduced via typical antibody clearance mechanisms in aged PDAPP mice treated with murine surrogate mE8c in a dose-and effector-function dependent manner. Notably, in both PDAPP mice and AD patients, the prevalence of the Aβp3-42 peptide is quite low (0.6%) with respect to the overall amount of Aβ42 deposited (DeMattos et al., 2012). Apparently sufficient phagocytic clearance occurs to reduce Aβ42 plaque load in aged animals.

Secondary pharmacodynamic studies

Donanemab was not evaluated for Fc effector functions ADCC and CDC because the target N3pE peptide is extracellular and not expected to be directly associated with or bound to cells. This is agreed but the phagocytotic activity is thought to be mediated by ADCP,. Potential off-target effects have been evaluated in the tissue-cross reactivity study (see toxicology section).

Safety pharmacology programme

In line with ICH S6(R1), no dedicated safety pharmacology studies were conducted with donanemab. This is acknowledged. The safety pharmacology of donanemab was evaluated as part of a repeat dose toxicity study in cynomolgus monkeys. There were no effects of donanemab on the respiratory system, central nervous system, or cardiovascular system up to 100 mg/kg, the highest dose tested.

Pharmacodynamic drug interactions

No pharmacodynamic drug interaction studies were performed. This is acceptable.

2.5.3. Pharmacokinetics

The single dose pharmacokinetics (PK) of donanemab (LY3002813) has been characterized in male cynomolgus monkeys upon intravenous (IV) and subcutaneous (SC) administration. In addition, multiple dose toxicokinetics (TK) of donanemab was examined upon weekly IV administration, which is the intended clinical route, in male and female Cynomolgus monkey (6-wks).
The single dose PK of the murine surrogate of donanemab (mE8c) has been investigated upon subcutaneous (SC) administration in CD-1 mice and the multiple dose toxicokinetics (TK) of the murine mE8c upon weekly SC or intraperitoneal (IP) administration in aged transgenic PDAPP mouse model for 6-week up to 6-month.

Methods of analysis

Assays were developed for the evaluation of exposure and immunogenicity in the nonclinical studies. Donanemab and its murine surrogate mE8c were quantified using sandwich enzyme linked immunosorbent assays (ELISA) using conjugated HRP for detection. The provided validation reports, which included (among others) the evaluation of precision and accuracy (intra- and inter-assay), specificity, selectivity, and sample stability (long-term, freeze-thaw), demonstrate that the assays were suitable for quantification of donanemab in monkey serum (including incurred sample reanalysis), and that the assay for quantification of mE8c was suitable for detection in mouse serum and plasma.

For the detection of antibodies against donanemab (ADAs) in monkey serum, an ELISA immunoassay, including solid-phase extraction with acid dissociation (SPEAD) sample pre-treatment, was developed and validated. The sensitivity of the anti-donanemab ADA assay was found to be 54 ng/mL for the assay in monkey serum. Drug tolerance of donanemab was 25 µg/mL in the presence of 598 ng/mL ADAs in monkey serum, above which the presence of ADAs may be masked.

Absorption

Upon single dose intravenous (SD, IV) administration of 1 mg/kg of donanemab to male cynomolgus monkeys (n=3), the serum concentration profile was characterized by a biphasic distribution and elimination pattern. The exposure ($AUC_{0\text{-}672}$), total body clearance and volume of distribution were

1860 µg*h/mL, 0.53 mL/h/kg and 85.8 mL/kg, respectively. The terminal elimination half-life ($t_{1/2}$) was found to be approximately 1 week (173 h).

After SD IV administration of three different donanemab lots to male cynomolgus monkeys (1 mg/kg, n=3), no notable differences were observed among the three lots with respect to the serum exposure (AUC_{0-672}, 1710 - 1900 µg*h/mL), clearance (0.49 – 0.55 mL/h/kg), volume of distribution (107 – 119 mL/kg) and $t_{1/2}$ (168 – 192 h). Based on the drop in the serum PK profile, there was evidence of ADA formation in one of the 12 animals two weeks after SD IV dosing.

Following subcutaneous (SC) administration of 1 mg/kg donanemab, the mean maximal serum concentration (C_{max}) was found to be ~7 µg/ml and was observed 48 - 64 hours post-dose (t_{max}). The mean $t_{1/2}$ was approximately one week. The mean absolute bioavailability (F_{sc}) of donanemab for the SC route was found to be 91 – 100%.

In a 6-week repeat-dose toxicology study, 1, 10 and 100 mg/kg donanemab was administered once weekly IV to male and female cynomolgus monkeys (n=3). The serum toxicokinetics (TK) parameters were measured at D1 and D36 and showed no clear or consistent sex difference. Systemic exposure (AUC_{0-166} = AUC_{tau}) to donanemab was roughly dose proportional. Upon repeated administration, AUC_{tau} accumulation ratio's (AR) fell under two-fold (1.5 – 1.9), meaning accumulation was low. A mean terminal elimination half-life of approximately 295 hours was observed during the recovery phase (sexes-combined). The NOAEL in the monkey was determined to be the highest IV dose tested of 100 mg/kg/week. The corresponding serum AUC_{tau} at D36 was 142,500 µg*h/mL (sexes-combined), meaning a C_{avg} of 858 µg/ml donanemab.

There was a positive signal of ADA formation with one of the six animals dosed with 1 or 10 mg/kg and in four of the 12 animals dosed with 100 mg/kg in this study. Two of the ADA-positive animals in the high-dose washout group had a clearly different (lower) donanemab exposure profile.

The toxicokinetics (TK) of mE8c (the murine surrogate to donanemab) was assessed in aged PDAPP (APPV717F transgenic) mice and the single dose pharmacokinetics (PK) in CD-1 mice.

The murine surrogate mE8c was administered weekly (30, 100 mg/kg, SC) to aged PDAPP mice in a 6-month toxicology study, which was terminated early due to high mortality. At termination, only plasma samples from male mice were available, which showed high variability (CV 46% - 73%). The corresponding plasma concentration at D151/152 was 208 µg/mL (n=9) and 463 µg/mL (n=4), for the 30 and 100 mg/kg, respectively.

In a second 6-month toxicology study, mE8c was administered weekly to aged female PDAPP mice at lower doses of 1.5, 4 or 12.5 mg/kg (SC). At termination, 72 h after the last dose, plasma mE8c concentration were 27.8, 62.5 and 234.6 µg/mL, for the 1.5, 4 or 12.5 mg/kg, respectively.

In a 3-month microhaemorrhage study, mE8c was administered weekly IP (intraperitoneal) to aged male and female PDAPP mice at 12.5 mg/kg. At termination, 72 h after the last dose, plasma mE8c concentration was 82.2 µg/mL, for the 12.5 mg/kg.

In a 6-week toxicology study, mE8c was administered weekly to aged PDAPP mice at 10, 30 or 100 mg/kg (SC). At 48 h after the last dose, serum, instead of plasma, mE8c concentrations were 2.3, 8.7 and 272.1 µg/mL, for the 10, 30 and 100 mg/kg, respectively. It was noted that the serum concentrations are two to 100-fold lower than the plasma concentrations at similar doses, which is questioning the relevance of these serum mE8c determinations (see CD-1 mice comments below).

The single dose PK study in male CD-1 mice (10 mg/kg, n=4, SC) was used to compare the PK profile of three different mE8c lots, which were used in the 6-week and the two 6-month multiple dose toxicology studies in PDAPP mice, and to assess the extent of plasma versus serum exposure of mE8c. This PK study showed that mE8c serum total exposure (AUC_{0-336}) was comparable across the three

material lots. But it is noted that the inter-individual mE8c serum concentrations demonstrated high variability (CV% up to 73%) and were at 336 hrs post-dose still high (65% – 100% of Cmax), questioning the need for weekly administration. More importantly, however, mE8c concentrations in the plasma samples were 26 to 36-fold higher than in serum, which is suggested to be the result of a loss of recovery during processing from whole blood samples occurring with serum, but not with plasma.

Distribution

In accordance with ICH S6(R1), formal tissue distribution and protein binding studies were not conducted with donanemab.

The low serum volume of distribution in cynomolgus monkeys, ranging over the different IV studies between 75 and 119 ml/kg, suggests a distribution to blood and the extravascular fluid as it is within 2 to 4 times that of serum volume (45 mL/kg). This is consistent with the known biodistribution of monoclonal antibodies.

Donanemab transfer to maternal milk was not examined. However, as an IgG, donanemab would be expected to be present in the first milk.

Metabolism

No metabolism studies with donanemab were conducted in animals. The absence of metabolism studies is in accordance with ICH S6(R1).

Excretion

As donanemab is a monoclonal antibody, no renal excretion is anticipated due to its molecular size. Therefore, no specific studies to measure excretion of donanemab were conducted. The absence of excretion studies in accordance with ICH S6(R1).

Pharmacokinetic drug interactions

Drug-drug interaction at the PK level is highly unlikely for this type of product since biotechnology-derived substances do not metabolize via CYP P450 enzymes. In addition, the mechanism of action of donanemab is not expected to have an effect on CYP450 enzymes or on transporters.

2.5.4. Toxicology

Single dose toxicity

Donanemab toxicity after a single dose was not evaluated, in accordance with ICH S6(R1) and ICH M3.

Repeat dose toxicity

Repeat-dose toxicology GLP studies have been conducted with mE8c in the pharmacologically relevant, aged PDAPP mouse model. At start of dosing, the mice were at least 12 months of age to ensure the consistent presence of Aβ plaques. In addition, a 6-month (non-GLP) combined pharmacology/toxicology study was performed in aged female PDAPP mice. A 6-week GLP study was

conducted in cynomolgus monkeys treated with donanemab. All GLP studies conducted included expanded neuropathologic evaluation.

Monkey study

A 6-week repeat dose toxicity study in monkeys aged 2-4 years, which were given weekly slow bolus IV doses of donanemab up to 100 mg/kg, did not result in notable donanemab related findings. Given the absence of Aβ plaques, this is anticipated and demonstrates the typically absent off-target effects of therapeutic antibodies. Thus, the NOAEL was 100 mg/kg/week, corresponding to a safety margin of 9.7x based on C_{avg} compared to the exposure at the therapeutic human dose of 1400 mg/4 weeks.

Mouse studies

In the combined six month pharmacology/toxicology (non-GLP) study, there were no mE8c-related changes in haematology, clinical chemistry, organ weight, macroscopic or microscopic endpoints up to a dose of 12.5 mg/kg. Six to seven mice were found dead during the study in each treatment group. While a cause of death was not determined for these mice, mortality also occurred in the controls, and was therefore not considered compound-related.

In the 6-week and 26-week GLP study, there were no mE8c-related effects on mortality, clinical observations, body weight, food consumption, haematology, clinical biochemistry, ophthalmology, organ weight, gross pathology and histopathology (including expanded neuropathological evaluation) up to doses of 100 mg/kg. There was considerable mortality both in control animals and in all mE8c-treated groups, but the incidence and timing were not dose-related. Due to abundant mortality, the 26-week study was terminated after a treatment duration of five months in males and 4.6 months in females. The most common cause of deaths for all preterminal euthanasia animals, including controls, was related to malignant neoplasia of haemolymphatic tissue (lymphoma). Metastasis was noted in all preterminal euthanasia animals, most commonly seen in the liver, spleen, bone marrow, and/or lymph nodes. Lymphoma metastasis or hyperplasia was also a common necropsy finding in most other animals that were euthanised according to schedule. Taking into account that the incidence and severity of these findings did not seem to be test-article related, it is acknowledged that the observed mortalities were due to age-related pathologies. Changes in haematology and clinical biochemistry were described to be consistent with a neoplastic proliferation of immature cells of lymphoid origin, and most often correlated with histopathological findings of multicentric lymphoma. There was no clear dose-response relationship with mE8c for these clinical pathology results. Notably, there was no evidence of brain vascular changes indicative of microhaemorrhage, in contrast with the increased incidences of amyloid-related imaging abnormalities (ARIA) observed clinically. Overall, due to the lack of a clear relationship between mE8c and the observed pathologies, there were no mE8c-related findings. The NOAEL for mE8c in aged PDAPP mice was considered to be the highest dose of 100 mg/kg, which is 8-fold the highest dose tested in pharmacology studies.

Genotoxicity and carcinogenicity

The absence of genotoxicity studies is in line with ICH S6 (R1).

No carcinogenicity studies were conducted. A weight of evidence approach, based on the specificity of donanemab, the target biology, the composition of donanemab and repeat dose toxicity studies, suggests that donanemab has a negligible carcinogenic risk.

*Reproductive and developmenta*l toxicity

The applicant conducted a weight-of-evidence (WoE) approach to evaluate reproductive risk. Due to the high specificity of donanemab and the target biology, the applicant argues that there is no plausible mechanism for developmental or reproductive risk as result of N3pE-containing Aβ plaque removal. Based on literature, as well as on the pharmacology study performed in young PDAPP mice, it

is likely that the N3pE Aβ is not present at notable levels in brain amyloid plaque until late in life after reproductive function has declined. In addition, donanemab did not show binding to membrane epitopes in a tissue cross-reactivity assay in reproductive tissues. The applicant further supports the claim of low potential for reproductive toxicity by referencing other anti-Aβ immunotherapies which do not suggest reproductive toxicity. Furthermore, results from repeat dose studies with donanemab and mE8c, including stage-dependent qualitative evaluation of spermatogenesis in mice, did not reveal any notable findings in reproductive organs or effects that could result in reproductive concern. In addition, the intended clinical population (primarily elderly patients) is an important aspect of the WoE considerations. Risk minimisation based on the collection of adverse event data from any spontaneous reports of pregnancy, as proposed by the applicant, is acceptable, particularly as a pregnancy outcome registry is not feasible.

In a previous Scientific Advice procedure (EMA/SA/0000054826), CHMP did not agree that the assessment of reproductive and developmental risk was complete. The CHMP recommended to perform an additional TCR study on human foetal tissues to exclude the potential off-target binding in foetal tissues that were not included in the nonclinical studies performed so far.

The applicant did not agree to perform an additional TCR study on human foetal tissues as such a study would not provide data that could be meaningfully applied to the human risk assessment of donanemab based on the following considerations:

- Donanemab is highly specific for binding to a unique target, cyclized glutamate in amyloid plaque; it does not bind non-cyclized Aβ or soluble Aβ protein.

- The perceived need to evaluate foetal tissues presumes the possible existence of off-target binding to some transiently expressed foetal tissue that is not present in young animals. The likelihood that an off-target epitope is expressed solely in the foetus and not in adults is very low.

- Such a study would have traditional limitations of TCR studies, including the interpretation of the significance of any binding.

- There are extreme limitations in the availability of consistent and relevant (stage of development) foetal tissues. The most relevant stage of development would correspond to the third trimester (when potential placental transfer of mAb would occur). However, foetal tissue at the post-organogenesis stage would not be relevant for evaluating any potential for teratogenicity. In addition, all tissues included in available foetal TCR panels are greater than eight weeks in gestation, at which point organogenesis in the human is complete. A full complement of three donors per tissue is often not available, and foetal TCRs have less than half the number of tissues for evaluation as compared to an adult TCR.

Based on these arguments, it can be agreed that interpretation of the findings of a TCR study on human foetal tissue and their value to inform on potential risks is limited.

Thus, the overall WoE, based on binding specificity, target biology, repeat dose toxicity data and the intended patient population, indicates a low reproductive risk. Additional non-clinical in vivo studies are not considered to be informative.

Local tolerance

Local tolerance was evaluated as part of the repeat dose toxicity studies. Based on the cynomolgus monkey repeat dose toxicity study, donanemab is not expected to cause issues with local tolerance when injected intravenously, the recommended administration route in humans.

Other toxicity studies

Tissue cross-reactivity study

Cross-reactive binding of donanemab was characterized in a panel of human and cynomolgus monkey tissues at concentrations of 5 and 25 µg/mL. In human tissues, cytoplasmic staining of lymphocytes was observed in gut-associated lymphoid tissue of several parts of the intestinal tract, including the colon, small intestine, stomach, lymph nodes, spleen, and tonsil. Cytoplasmic staining of lymphocytes in monkeys was also seen in these tissues, and additionally in the bronchus-associated lymphoid tissue (BALT) of the lungs and in the thymus. Donanemab staining unique to cynomolgus monkey tissues included myelin in the peripheral nerve, and nuclei in adrenal medulla, cerebellum of the brain, and testis. In addition, donanemab-specific nuclear and/or cytoplasmic staining in monkeys was observed in various cell types in the thyroid, fallopian tubes, and pituitary. The intensity and presence of donanemab-specific staining in cynomolgus monkeys appeared concentration-related. Since donanemab would not be expected to enter cells in vivo, nuclear and cytoplasmic staining in these tissues was not considered to be toxicologically relevant. It should be noted that minimal to moderate myelin staining of axons surrounding the peripheral nerves was observed in all three samples of both concentrations. It was not described whether this was membranous, nuclear or cytoplasmic. However, myelin staining was not observed in human tissues, hence the clinical relevance may be limited.

Microhaemorrhage Evaluation

Previous studies have demonstrated that treatment of aged PDAPP transgenic mice with certain anti-Aβ antibodies leads to an increase in cerebral amyloid angiopathy (CAA)-associated microhaemorrhage. The potential of Aβp3-X antibodies to exacerbate cerebral amyloid angiopathy (CAA)-associated microhaemorrhage (MH), due to its plaque lowering mechanism of action, was evaluated in a 3-month study with PDAPP mice aged 23 to 24 months. Since CAA, which is identified by enrichment of Aβ1-40 in isolated brain vessels, is not apparent in mice younger than 21 months of age, evaluation of MH was not evaluated in the 6-month repeat-dose studies in PDAPP mice. While treatment of aged PDAPP transgenic mice with 3D6 substantially increased microhaemorrhage, treatment with mE8 or mE8c did not exacerbate microhaemorrhage at a dose that lowered deposited Aβ in these animals (12.5 mg/kg), except for one outlier. These results suggest that the removal of amyloid plaques is not associated with exacerbation of CAA-related microhaemorrhage in aged PDAPP mice up to three months of dosing. In contrast, amyloid-related imaging abnormalities (ARIAs) were observed in clinical studies with donanemab.

2.5.5. Ecotoxicity/environmental risk assessment

As a recombinant protein, donanemab is not anticipated to pose a risk to the environment. Further evaluation of environmental risk is not needed, in line with the Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use. The active substance is a natural substance, the use of which will not alter the concentration or distribution of the substance in the environment. Therefore, donanemab is not expected to pose a risk to the environment.

2.5.6. Discussion on non-clinical aspects

Pharmacology

The target of donanemab is the $A\beta_{p3\text{-}x}$ peptide, also referred to by the applicant as N3pG or N3pE. N3pE mAbs are developed as anti-$A\beta_{p3\text{-}X}$ antibodies, recognizing both Aβp3-40 and Aβp3-42. This was confirmed by SPR (Aβp3-42) and Western blot and ELISA experiments (Aβp3-40).

N3pE is a modified form of Aβ expected to be only found in deposited Aβ plaques but not in soluble Aβ. Antibodies targeting forms of Aβ only present in plaque were hypothesized to be more effective compared to other Aβ mAbs as they do not become saturated with soluble Aβ. Upon request, the applicant provided additional data to demonstrate that the target is insoluble and only present in deposited plaques. In extracts from AD patients brain, no detectable Aβp3-42 was observed in PBS extracts (soluble Aβ), although it should be noted that the detection limit was not described. In contrast, in guanidine extracts (insoluble/deposited Aβ), the Aβp3-42 peptide was detected. In addition, the applicant investigated the presence of Aβp3-x in CSF of AD patients. The resulting western blot with mE8c (anti-Aβp3-x) demonstrated no Aβp3-40 or Aβp3-42 in CSF below the detection limit of ~8 pg/ml, which was stated to be 300-fold lower than for Aβ1-42. Furthermore, evaluation of immunoprecipitated plasma in aged PDAPP mice after treatment for four 12.5mg/kg injections every 3 days treated with either mE8c, 1A1 (anti-Aβ13-28), or mE8c+1A1 revealed no detectable Aβp3-40 or Aβp3-42 peptide levels in plasma below the detection limit of ~13pg/ml, which is ~4-fold lower than steady-state plasma levels of Aβx-42. Furthermore, Aβ1-42 was not detected in plasma following mE8c treatment alone, indirectly supporting the lack of binding affinity for the full length Aβ. Overall, given the absence of detectable Aβp3-42 in soluble AD brain extracts, the absence of detectable Aβp3-40 and Aβp3-42 in CSF of AD patients and the absence of measurable Aβp3-40 and Aβp3-42 in plasma of aged PDAPP mice, the presented results are indicative of the insolubility and plaque specificity of Aβp3-40 and Aβp3-42. However, given the semi-quantitative nature of western blot experiments, the exact amounts in plasma or CSF are unknown. Therefore, it can also not be completely ruled out that some of the epitope is soluble. Nevertheless, considering the low prevalence of the Aβp3-42 peptide (1%) with respect to the overall amount of Aβ42 deposited, the presence in plasma is presumably also quite low compared to the full length peptide.

Donanemab antibody-mediated clearance of N3pE involving the engagement of Fcγ receptors to perform ADCP is a plausible mode of action. Upon request, the applicant provided an overview of *in vitro* data on donanemab binding to FcR isoforms.

The murine parental antibody mE8c exhibited a binding affinity (KD) for N3pE Aβ of <0.2 nM and donanemab of 0.82 nM. Neither of these antibodies bind to human $A\beta_{1-40}$ peptide at concentrations up to 1 μM. The applicant was asked to also demonstrate (the lack of) binding to $A\beta_{1-42}$, or otherwise provide an adequate justification why this was not evaluated. The applicant indicated that because of the non-specific binding characteristics of Aβ1-42, SPR was not a suitable approach for characterisation of interactions between donanemab or mE8c and Aβ1-42. This argument was not further elucidated. In line, mE8 also demonstrated a substantially higher binding activity towards both the Aβp3-40 and Aβp3-42 peptides over the full-length Aβ1-40 or Aβ1-42, as evaluated by ELISA.

Ex vivo studies with AD brain slices suggest that a potential mE8c mediated clearance mechanism involves microglia-mediated phagocytosis. *In vivo* target engagement studies suggested that both mE8 and human N3pE antibodies engaged deposited target *in vivo* throughout the hippocampus and cortical regions results would suggest that the antibodies are able to pass the blood-brain-barrier (BBB) in mice and are able to engage with the target, but the relevance for the clinical situation is unclear due to different study lengths (three weeks with mE8 versus three days with human anti-N3pE antibodies) and hence differences in already cleared Aβ, and mouse/human BBB differences. *In vivo* proof of concept studies demonstrated that treatment with mE8c reduced plaque load in the hippocampus and cortex of aged PDAPP mice, while no significant effect was shown in a prevention study in young PDAPP mice.

Increases in plasma $A\beta_{1-40}$ was described to be an in vivo surrogate for antibody binding to physiological levels of endogenous $A\beta_{1-40}$. However, the claim, by the applicant that the m266 antibody becomes saturated in vivo with full length Aβ cannot be supported based on this study. Given the presented data, control antibody m266 is unlikely to be saturated with soluble $A\beta_{1-40}$, since free m266

IgG was at least 200-fold more present in plasma than m266 that was bound to 2 nM $A\beta_{1-40}$. Moreover, the applicant was also asked to discuss why plasma accumulation was not evaluated for $A\beta_{1-42}$, especially since also no in vitro binding data for this Aβ form was presented and since the vast majority of deposited Aβ in PDAPP mice constitutes $A\beta_{1-42}$. The applicant referred to DeMattos et al. (2012) in which plasma levels of both Aβx-40 and Aβx-42 were evaluated. ELISA analysis on plasma revealed significantly elevated levels of Aβx-40 and Aβx-42 in 3D6-treated mice but no difference in the mE8- or control-treated mice. The applicant indicates that plasma Aβ accumulation is thought to reflect reduced rates of clearance from blood due to the antibody binding. Although this suggestion was not further substantiated by pharmacokinetic data, these results further demonstrate that the mE8 and mE8c antibodies do not bind to soluble full-length Aβx-40 or Aβx-42.

Overall, the proof of concept has been sufficiently demonstrated. Donanemab binds to N3pE containing amyloid beta plaques, which were demonstrated to be reduced via typical antibody clearance mechanisms in aged PDAPP mice treated with murine surrogate mE8c in a dose-and effector-function dependent manner. It is noted that the primary hypothesis is that removal of Aβ plaques is believed to slow cognitive impairment. Upon request, the applicant explained that given the limitations of behavioural assessments in PDAPP mice (including Aβ-independent memory improvement) and the lack of translation to the clinic for several other anti-Aβ immunotherapies using other APP transgenic mice in which in addition to amyloid removal, beneficial behavioural effects were demonstrated, the applicant focused on microglial-mediated plaque removal as a primary pharmacological endpoint. This argumentation can be followed. Notably, also the relevance of the PDAPP mice to the pathogenesis of AD, according to the applicant, is unclear and appears limited given the lack of prominent tau pathology or neurodegeneration.

Regarding secondary pharmacodynamics, donanemab was not evaluated for Fc effector functions ADCC and CDC because the target N3pE peptide is extracellular and not expected to be directly associated with or bound to cells.

In line with ICH S6(R1), no dedicated safety pharmacology studies were conducted with donanemab.

No pharmacodynamic drug interaction studies were performed.

Pharmacokinetics

Two animal species have been used in pre-clinical testing: monkey for donanemab (IV, SC) and mouse for mE8c (SC, IP). ELISA's were developed and validated for the evaluation of exposure and immunogenicity of donanemab in monkey serum and of mE8c exposure in mouse serum and plasma.

The monkey SD PK studies revealed a low clearance (0.5-0.6 ml/h,kg), about 1.5-fold higher than the human clearance, and a terminal elimination half-life $t_{1/2}$ of about 7 days upon SD and 12.3 days after multiple dosing, which is in line with the $t_{1/2}$ in humans (12.2 days). Monkeys dosed weekly with donanemab showed an almost dose-proportional increase in exposure and limited accumulation over time (AR ≤2.0), with 16% up to 33% at the high dose of ADA formation without clear or consistent differences between sexes.

In mouse, SD PK in CD-1 and MD (weekly) TK studies in PDAPP, mE8c was dosed SC for six weeks, three months (IP) and six months. In the MD TK exposure to mE8c was only assessed at a single time point at the end of the dosing period.

In an 6-month toxicology study, mE8c was administered weekly to aged female PDAPP mice at 1.5, 4 or 12.5 mg/kg (SC). Upon request, the applicant supplied the individual animal data, that were used to calculate the mean antibody concentrations (µg/mL) of the aged female PDAPP mice study described in report NDG78.

Plasma mE8c concentrations in the CD-1 mouse study (SD PK) were 26 to 36-fold higher than in serum, which is suggested to be the result of a loss of recovery during processing from whole blood samples. This phenomenon has not been further investigated but it is speculated that an interaction with fibrin components during the clotting process may be responsible for the lower serum mE8c levels in the mouse. The relevance of all mouse mE8c serum values is questioned as more than 96% of the mE8c is lost during processing and that this seems to be mE8c concentration dependent since in the six week PDAPP mouse toxicology study the plasma/serum ratio ranges from 100- to two-fold with increasing dose. But given that in most mice studies plasma was used, the impact is considered minimal. As donanemab has a similar specificity, the impact for other species (mouse vs monkey/human) and/or a potential secondary target binding specificity of mE8c versus donanemab inducing this phenomenon was discussed. A similar low serum recovery effect was, however, not found with donanemab in cynomolgus monkey, nor in spiked human serum versus plasma determination.

Toxicology

Repeat-dose toxicology GLP studies have been conducted with mE8c in the pharmacologically relevant, aged PDAPP mouse model and the cynomolgus monkey was used as non-rodent test species for a 6-week GLP repeat dose toxicology study. The applicant selected the cynomolgus monkey as non-rodent test species because the cynomolgus monkey is widely accepted as non-rodent toxicology model, particularly for monoclonal antibodies. While this choice would be understood if the animals assigned to the study were aged in order to allow the possibility of target engagement, it is acknowledged that such animals would be difficult to source. Nevertheless, it is questioned why donanemab was evaluated in prepubertal monkeys not displaying Aβ pathology. Off-target effects could have also been assessed using another non-rodent species as it is unlikely that prepubertal monkeys would express Aβ to allow a pharmacological interaction with donanemab.

The 6-week monkey study did not result in notable donanemab related findings up to 100 mg/kg/week. Given the absence of Aβ plaques, this is anticipated and demonstrates the typically absent off-target effects of therapeutic antibodies.

In the 6-week and 26-week GLP study in PDAPP mice, there were no mE8c-related effects up to doses of 100 mg/kg. There was considerable mortality both in control animals and in all mE8c-treated groups, but the incidence and timing were not dose-related. The most common cause of deaths for all preterminal euthanasia animals, including controls, was related to malignant neoplasia of haemolymphatic tissue. Taking into account that the incidence and severity of these findings did not seem to be test-article related, it is acknowledged that the observed mortalities were due to age-related pathologies. Overall, due to the lack of a clear relationship between mE8c and the observed pathologies, there were no mE8c-related findings. The NOAEL for mE8c in aged PDAPP mice was considered to be the highest dose of 100 mg/kg, which is 8-fold the highest dose tested in pharmacology studies.

The absence of genotoxicity studies is in line with ICH S6 (R1). No carcinogenicity studies were conducted. A weight of evidence approach suggests that donanemab has a negligible carcinogenic risk.

The applicant conducted a weight-of-evidence (WoE) approach to evaluate reproductive risk. Due to the high specificity of donanemab and the target biology, the applicant argues that there is no plausible mechanism for developmental or reproductive risk as result of N3pG-containing Aβ plaque removal. Based on literature, as well as on the pharmacology study performed in young PDAPP mice, it is likely that the N3pG Aβ is not present at notable levels in brain amyloid plaque until late in life after reproductive function has declined. In addition, donanemab did not show binding to membrane epitopes in a tissue cross-reactivity assay in reproductive tissues. The applicant further supports the claim of low potential for reproductive toxicity by referencing other anti-Aβ immunotherapies which do not suggest reproductive toxicity. Furthermore, results from repeat dose studies with donanemab and

mE8c, including stage-dependent qualitative evaluation of spermatogenesis in mice, did not reveal any notable findings in reproductive organs or effects that could result in reproductive concern. In addition, the intended clinical population (primarily elderly patients) is an important aspect of the WoE. Although it is not very likely that women of childbearing potential (WoCBP) will be treated with donanemab, it can also not be completely excluded. There could be a very small number of WoCBP with early onset AD who might benefit from treatment with donanemab. Thus, the overall weight-of-evidence, based on binding specificity, target biology, repeat dose toxicity data and the intended patient population, indicates a low reproductive risk. Additional non-clinical in vivo studies are not considered to be informative.

2.5.7. Conclusion on the non-clinical aspects

There are no objections to marketing authorisation from a non-clinical point-of-view.

2.6. Clinical aspects

2.6.1. Introduction

GCP aspects

The clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the Community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

Table 1. Tabular overview of clinical studies

Study ID **No. of study centres/ locations** **Study period**	**Design** **Objective** **Duration**	**Dose at study initiation**	**Subjects by arm (ITT)**	**Male/Female** **Age (range)** **APOE-ε status** **Diagnosis (Mild AD/MCI)**	**Efficacy endpoints**
I5T-MC-AACD 8 centres: US /JAP Dec 2015- Jul 2020	Phase 1b RD DB PC SD MAD Safety, tolerability, PK and PD SD: one dose + FU 24 weeks MAD: Q2W PC: 24 weeks + FU 24 weeks Q4W: 72 weeks + FU 12 weeks	SD: 10 mg/kg IV 20 mg/kg IV 40 mg/kg IV MAD: 10 mg/kg Q2W IV 20 mg/kg Q2W IV 10 mg/kg Q4W IV 20 mg/kg Q4W IV	SD: Placebo: 7 10 mg/kg IV: 7 20 mg/kg IV: 7 40 mg/kg IV: 4 MAD: Placebo: 3 10 mg/kg Q2W IV: 10 20 mg/kg Q2W IV#: 0 Placebo: 5 10 mg/kg Q4W IV: 8 20 mg/kg Q4W IV: 10	27/34 74 (54-90) MCI Mild AD Moderate AD Not described which subjects had which diagnosis.	Primary: Reduction of cerebral amyloid load from BL at Weeks 12, 24, 36, 48 and 72 Secondary: Safety parameters PK parameters ADA's and Nab's
I5T-MC-AACG 56 centres: US /CAN Dec 2017- Dec 2020	Phase 2 RD DB PC Efficacy and safety PC: 76 weeks LTE: up to 48 weeks (=Study AACH)	Dose 1-3 : 700mg Q4W IV ⩾3rd dose : 1400mg Q4W IV	Total: 272 placebo: 126 donanemab: 131 donanemab- BACE combi*: 15	127/145 75 (61-86) Carrier: 73% Noncarrier: 29% MCI (MSSE 27-28): 51 Mild AD (MMSE 20-26): 176 Number of subjects not clearly reported	Primary: Δ from BL in iADRS at Week 76 Secondary: Δ from BL at Week 76 in: CDR-SB ADAS-COG13 ADCS-ADL-MCI MMSE Brain amyloid load
I5T-MC-AACI 277 centres: US/EUR/CAN/ Japan Jun 2020- Apr 2023	Phase 3 RD DB PC Efficacy and safety PC: 76 weeks LTE: 78 weeks FU: 44 weeks	Dose 1-3: 700mg Q4W IV ≥3rd dose: 1400mg Q4W IV	Total: 1736 Placebo: 876 donanemab: 860	740/996 73 (59-86) Carrier: 70.5% Noncarrier: 29.5% MCI (MSSE 27-28): 83(16.3%) Mild AD (MMSE 20-26): 1451 (83.6%)	Primary** : Δ from BL in iADRS at Week 76 Secondary** : Δ from BL at Week 76 in: CDR-SB ADAS-COG13 ADCS-ADL-MCI MMSE Brain amyloid load

20 mg/kg IV Q2W for 24 weeks was not initiated.
*Under previous versions of the protocol donanemab was administered in combination with 12 mg of a BACE inhibitor. However, the combination therapy was discontinued from the study. Patients in this group in remained blinded and were allowed to continue in the study, receiving monthly infusions of donanemab without the co administration of the oral agent.
**Endpoints investigated in both low-medium ('intermediate') tau population and overall population
AD = Alzheimer's Disease, ADA= anti-drug antibodies, ADAS-Cog13 = Alzheimer's Disease Assessment Scale – Cognitive 13-Item Scale, ADCS-ADL-MCI = Alzheimer's Disease Cooperative Study – Activities of Daily Living – Mild Cognitive Impairment, AUS = Australia, BL= baseline, CAN = Canada, CDR-SB = Clinical Dementia Rating-Sum of Boxes, DB = double-blind, EUR = Europe, FU = follow-up, iADRS = integrated Alzheimer's Disease Rating Scale, HV = healthy volunteers, ITT = intent-to-treat, LTE = long term extension, MAD = multiple ascending dose, MCI = Mild Cognitive Impairment, MMSE = Mini-Mental State Examination, Nab = neutralizing ADA, OLE = open label extension, PC = placebo-controlled, PET = positron emission tomography, PL = placebo, SD = single dose, RD = randomised, US = United States, Δ = change.

2.6.2. Clinical pharmacology

Donanemab is a monoclonal antibody designed to target an insoluble, modified, N-terminal truncated form of amyloid beta (N3pG Aβ). Donanemab has been administered in four completed clinical studies: (AACC), I5T-MC-AACD (AACD), I5T-MC-AACG (AACG), and the placebo-controlled part of I5T-MC-AACI (AACI-PC).

Ongoing studies include Part B of Study I5T-MC-AACH (AACH), the long-term extension study period of Study I5T-MC-AACI (AACI-LTE), and Safety Addendum of Study I5T-MC-AACI (AACI-Safety Addendum). The studies included in the clinical pharmacology programme are shown in Table 9.

Studies AACC and AACD were single- and multiple-ascending dose studies designed to evaluate safety, PK, PD, and immunogenicity in participants with mild cognitive impairment due to AD or mild to moderate AD. Doses administered were between 0.1 – 40 mg/kg (SD) and 10 – 20 mg/kg (MD). Study AACC also included one single cohort of young healthy volunteers in addition to the cohorts of participants with AD for a dose of 1 mg/kg. In addition, one patient cohort received donanemab via subcutaneous infusion.

Study AACG was a Phase 2 study evaluating the efficacy of donanemab in participants with early symptomatic AD following a titration regimen of 700 mg every four weeks for three doses, followed by 1400 mg every four weeks with a possibility of down-titration.

Study AACH Part B will provide (not submitted yet) additional safety and clinical information as an open-label study in participants who were assigned placebo in Study AACG. These participants receive a titration regimen of 700 mg every four weeks for three doses, followed by 1400 mg every four weeks. Participants remain on 1400 mg every four weeks for the rest of study or discontinue donanemab when their amyloid reduction meets the eligibility criteria for completing active treatment.

Phase 3 Study AACI includes both a placebo-controlled period (AACI-PC) and a long-term extension period (AACI-LTE). Donanemab was given at a dose of 700 mg every four weeks for three doses, followed by 1400 mg every four weeks. Participants remain on 1400 mg every four weeks for the rest of study or they may switch to placebo when their amyloid reduction meets the eligibility criteria for completing active treatment.

Study AACI-Safety Addendum will collect (not submitted yet) open-label exposure and safety data in participants with early symptomatic AD who have confirmed brain amyloid pathology measured by amyloid PET. Donanemab is given at a dose of 700 mg every four weeks for three doses, followed by 1400 mg every four weeks. Participants remain on 1400 mg every four weeks for the rest of study or discontinue donanemab when they meet the eligibility criteria for completing active treatment.

Table 2. Studies in clinical pharmacology programme

Study	Phase	Objective(s)
I5T-MC-AACC	1	To assess safety, tolerability, and PK profile of single and multiple IV doses of donanemab.
I5T-MC-AACD	1b	To assess safety, tolerability, PK, and PD profiles of single and multiple IV doses of donanemab.
I5T-MC-AACG	2	To evaluate safety and efficacy of donanemab and assess whether removal of existing amyloid plaque can slow the progression of AD in up to 72 weeks of treatment.
I5T-MC-AACH	2	Part B: To evaluate safety and tolerability of donanemab, to assess the effect of donanemab on clinical progression, brain amyloid deposition, and brain region volumes, and to assess peripheral PK and presence of anti-donanemab antibodies Part C assesses the long-term effect of donanemab on PET imaging biomarkers, cognition, and functioning in participants who have not received IP for at least 52 weeks
I5T-MC-AACI (Placebo Controlled)	3	To assess effect of donanemab on clinical progression of AD, brain amyloid deposition, brain tau deposition, and brain region volumes, to evaluate the safety and tolerability of donanemab, and to assess peripheral PK and presence of anti-donanemab antibodies.
I5T-MC-AACI (Safety Addendum)	3	To evaluate safety and tolerability of donanemab, to assess peripheral PK and presence of anti-donanemab antibodies, and to assess effect of donanemab on brain amyloid deposition and blood-based biomarkers.

Abbreviations: AD = Alzheimer's disease; IV = intravenous; PD = pharmacodynamic; PK = pharmacokinetic.

2.6.2.1. Pharmacokinetics

Analytical methods

The bioanalytical method validation indicated that accuracy and precision were acceptable, the method was selective under normal, lipemic and haemolytic conditions, hook effect was not observed, dilution linearity was acceptable, and stability was sufficient under different conditions. Samples were stable between -60 ºC and -80ºC for at least 631 days. Samples were also analysed within this time period. Incurred sample analysis was reported and within limits as defined in ICH M10. Accuracy and precision in the study reports was largely similar compared to values reported in the method validation report.

Several assays were performed for the validation of the UFAT-ACE Bridge assay procedure, which was used to quantify anti-donanemab antibodies in human serum. Analysis of precision, stability, ruggedness, titre determination, cut point evaluation, serum factor interference, irrelevant antibody effect, and sensitivity were acceptable. The assay is sufficiently drug tolerant. 100 ng/mL positive control ADA in the presence of up to 99.1 µg/mL of donanemab can be detected, which is higher than nearly all of the observed trough concentrations. A high percentage of ADA positive subjects is reported, which allows evaluation of ADA effect on PK and PD.

PopPK model

The objectives of the population PK/PD analysis are to

- characterize the PK of donanemab in patients with early symptomatic AD
- identify patient or other factors that impact the PK of donanemab
- characterize the dose-/exposure-response relationships
- identify potential factors that may impact the dose-/exposure-response relationship
- explore potential covariates, such as demographic factors, laboratory parameters, immunogenicity, baseline tau burden, baseline amyloid PET, prior and concomitant therapies, and disease characteristics that may influence donanemab disposition in this patient population
- generate model-predicted estimates of donanemab exposure to support subsequent efficacy and safety analyses, and

- explore clinical application of any findings above through simulations.

The PK dataset contained 22,288 observations from 2131 participants (46 participants from Study AACD, 131 participants from Study AACG, 54 participants from Study AACH, Part B, and 1900 participants from AACI [PC and Safety Addendum]). The population pharmacokinetic dataset was analysed using nonlinear mixed effects modelling NONMEM. The concentration-time data was fit to provide estimates of the population pharmacokinetic parameters and error terms. First order conditional estimation (FOCE) was used as the estimation method for the NONMEM analysis. Due to the relatively frequent occurrence of values below the quantifiable lower limit of the assay, the M3 approach was used in the PK analysis.

The selected base model has two compartments following IV infusion, with interparticipant variability on CL, as well as central and peripheral volumes of distribution. Additionally, clearance and distributional clearance were scaled allometrically by weight, and central and peripheral volumes of distribution were also scaled allometrically with weight, using exponents of 0.8 for clearance terms and one for volume terms. Following the completion of stepwise covariate modelling and additional covariate testing outside stepwise covariate modelling, one covariate effect was found to be statistically significant. The final model includes covariate effect of titre change over time on clearance (Table 3, Figure 1).

Table 3. PK and covariate parameters of the final popPK model

Parameter	Base Model Population Mean (95% CI)[a]	Final Model Population Mean (95% CI)[a]
CL (L/h)[b]	0.0300 (0.0288, 0.0320)	0.0255 (0.0243, 0.0271)
V1 (L)[c]	3.40 (3.35, 3.44)	3.36 (3.31, 3.40)
V2 (L)[d]	4.48 (3.94, 5.25)	4.83 (4.26, 5.73)
Q (L/h)[e]	0.0196 (0.0166, 0.0247)	0.0200 (0.0163, 0.0248)
Covariate effects		
Covariate effect on CL		
Effect of titer	NA	0.0487 (0.0436, 0.0552)
Between-participant variability CV% (95% CI)[a, g]		
CL	28.6% (26.6, 30.4)	24.9% (23.1, 26.8)
V1	18.7% (14.6, 23.1)	18.7% (14.7, 22.7)
V2	74.6% (67.2, 81.5)	93.9% (81.8, 109)
Residual unexplained variability		
Proportional (%)	46.9% (45.5, 48.2)	44.4% (43.3, 45.4)
Additive (ng/mL)	94.0 (79.4, 109)	91.5 (79.5, 106)

Abbreviations: CI = confidence interval; CL = clearance; CV = coefficient of variation; NA = not applicable; V1 = volume of distribution, central compartment; V2 = volume of distribution, peripheral compartment; Q = intercompartment clearance; WT = weight at baseline.

Note: numbers specified in the relationships below refer to the final model.

[a] 95% CI from bootstrap.

[b] $0.0255 * (WT/72)^{0.5}$.

[c] $3.36 * (WT/72)^{1.0}$.

[d] $4.83 * (WT/72)^{1.0}$.

[e] $0.0200 * (WT/72)^{0.5}$.

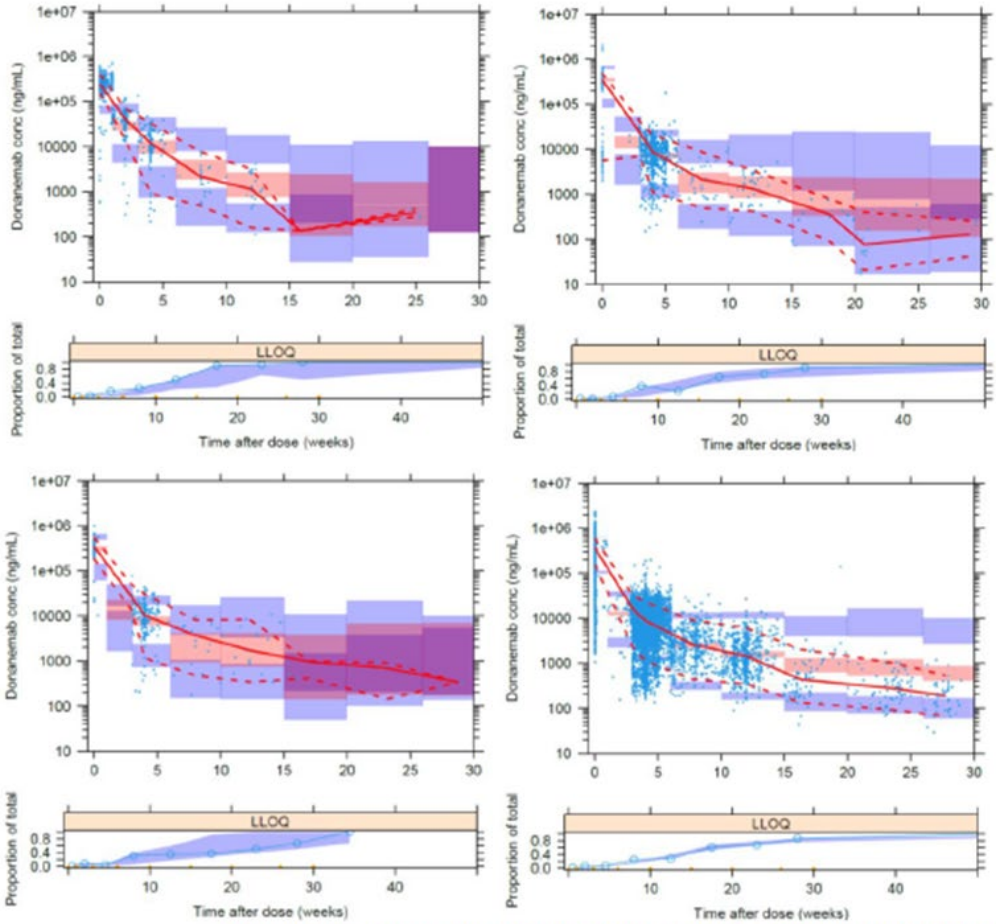
[f] $0.0255 * (WT/72)^{0.5} * (1 + ((0.0487*\ln(titer(t)))$.

[g] Between-participant variability was calculated using the following equation for log-normal distributions of the random effects $\%CV = 100 \times \sqrt{(e^{OMEGA_N} - 1)}$, where $OMEGA_N$ is the variance of the parameter.

Eta shrinkage base model: CL = 12.4%, V1 = 38.2%, V2 = 21.8%.

Eta shrinkage final mode: CL = 15.1%, V1 = 36.7%, V2 = 17.9%.

Figure 1. Visual predictive check of the final popPK model



Abbreviations: AACD = Study I5T-MC-AACD; AACG = Study I5T-MC-AACG; AACH = Study I5T-MC-AACH; AACI = Study I5T-MC-AACI; CI = confidence interval; LLOQ = lower limit of quantification.
Solid red line: median of observed concentrations; dashed red lines: 5th and 95th percentiles of observed concentrations; red shaded area: confidence interval for the median of simulated data; blue shaded areas: confidence intervals for the 5th and 95th percentiles of simulated data; blue full circles: individual observed concentration data; yellow ticks: data binning. Bottom panel: the proportion of concentration data below the LLOQ vs time. The blue area represents the 95% CI of the proportion of simulated concentrations below the LLOQ. In the simulation, LLOQ data were modeled using the M3 method.

IADRS and CDR-SB model

Separate models were developed for clinical outcomes CDR-SB and iADRS. Treatment effect models driven by dosing information of donanemab were tested as a predictor of disease progression. A concentration-effect relationship could not be identified in the IADRS and CDR-SB PK-PD models, as only one dosing regimen was studied in Studies AACG and AACI. Covariate effects were assessed in the donanemab treatment effect model.

- Immunogenicity was not found to have a statistically significant effect on response to donanemab.
- Baseline tau group had a statistically significant impact on treatment effect.
- No other covariate effects (age, gender, TE ADA, ADA titre, time since onset of symptoms or diagnosis with AD, or body weight at baseline) had a statistically significant impact on treatment effect.
- Baseline score and disease progression rate were influenced by multiple covariates. Specifically, disease status (with baseline MMSE), baseline tau group, gender, age, and time since AD diagnosis were covariates on baseline score.

- disease progression rate was impacted by age, APOE ε4 carrier status, baseline MMSE, and baseline tau group.

Disease progression rate estimated using exposure-amyloid plaque-scores model on iADRS was reduced by 33.2% (p<.001), while progression as measured by CDR-SB was reduced by 36.3% (p<.001) in the low/medium tau population. In the combined population, disease progression rate on iADRS score was reduced by 29.3% (p<.001), while progression as measured by CDR-SB was reduced by 31.7% (p<.001).

Absorption

Donanemab is administered by IV infusion and Cmax is achieved at the end of infusion.

Distribution

Donanemab follows a two-compartment disposition after IV administration. Central volume of distribution is slightly larger than plasma volume (mean of 3.36 L with between participant variability of 18.7%) and peripheral volume of distribution of 4.83 L with between-participant variability of 93.9%.

The observed CSF to serum concentration ratio was approximately 0.00208 (0.208%) across all participants and dose levels.

Elimination

Donanemab is a monoclonal antibody and is expected to be degraded into small peptides and amino acids via catabolic pathways in the same manner as an endogenous immunoglobulin G, hence there is no active metabolite formation or metabolic inhibition or induction of enzymatic pathways. It is also not expected to be metabolized by the cytochrome P450 families of drug-metabolizing enzymes responsible for metabolism and elimination of small molecules and would, therefore, not cause cytochrome P450-mediated clinical drug-drug interactions as a victim drug.

Based on the population PK analysis, clearance is 0.0255 L/h with between-participant variability of 24.9%. The estimated terminal elimination half-life is approximately 12.1 days for a typical participant with weight of 72 kg and maximum ADA titre of 1:2560.

Dose proportionality and time dependencies

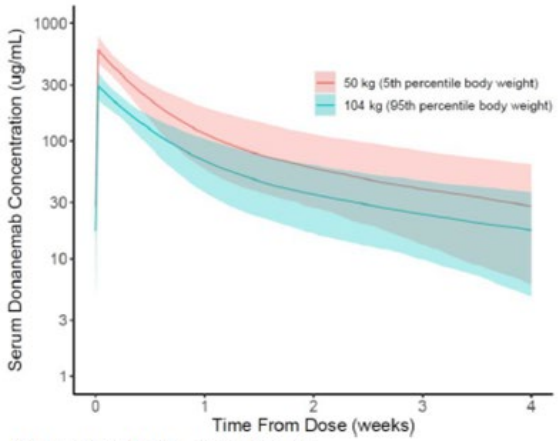
For single doses below 10 mg/kg (approximately 700 mg), Cmax values of donanemab across dose groups were proportional to the dose. After single-dose administration ranging from 0.1 to 3 mg/kg, the mean terminal elimination half-life was about 4 days, increasing to around 10 days at the 10-mg/kg dose level. In doses from 10 to 40 mg/kg, AUC(0-∞) and Cmax were approximately dose proportional following single doses. At doses of 10 and 20 mg/kg, $AUC_{T,ss}$ and $C_{max,ss}$ were approximately dose proportional at steady state. The PK of donanemab seems linear with respect to time at the 10- to 20-mg/kg dose levels. No accumulation of donanemab was observed with the 10-mg/kg Q4W dose, with a relative accumulation (RA) of approximately 1. There was limited accumulation with the 20-mg/kg Q4W dose, with a mean RA of 1.26.

Special populations

Donanemab PK was not influenced by age (54 to 88 years at study entry), gender (55.0% female), race (89.9% white, 6.3% Asian, 2.9% black, 0.3% American Indian or Other), Cockcroft-Gault creatinine clearance (8.1 to 179.9 mL/min), hepatic status, or APOE ε4 carrier status (66.4% positive).

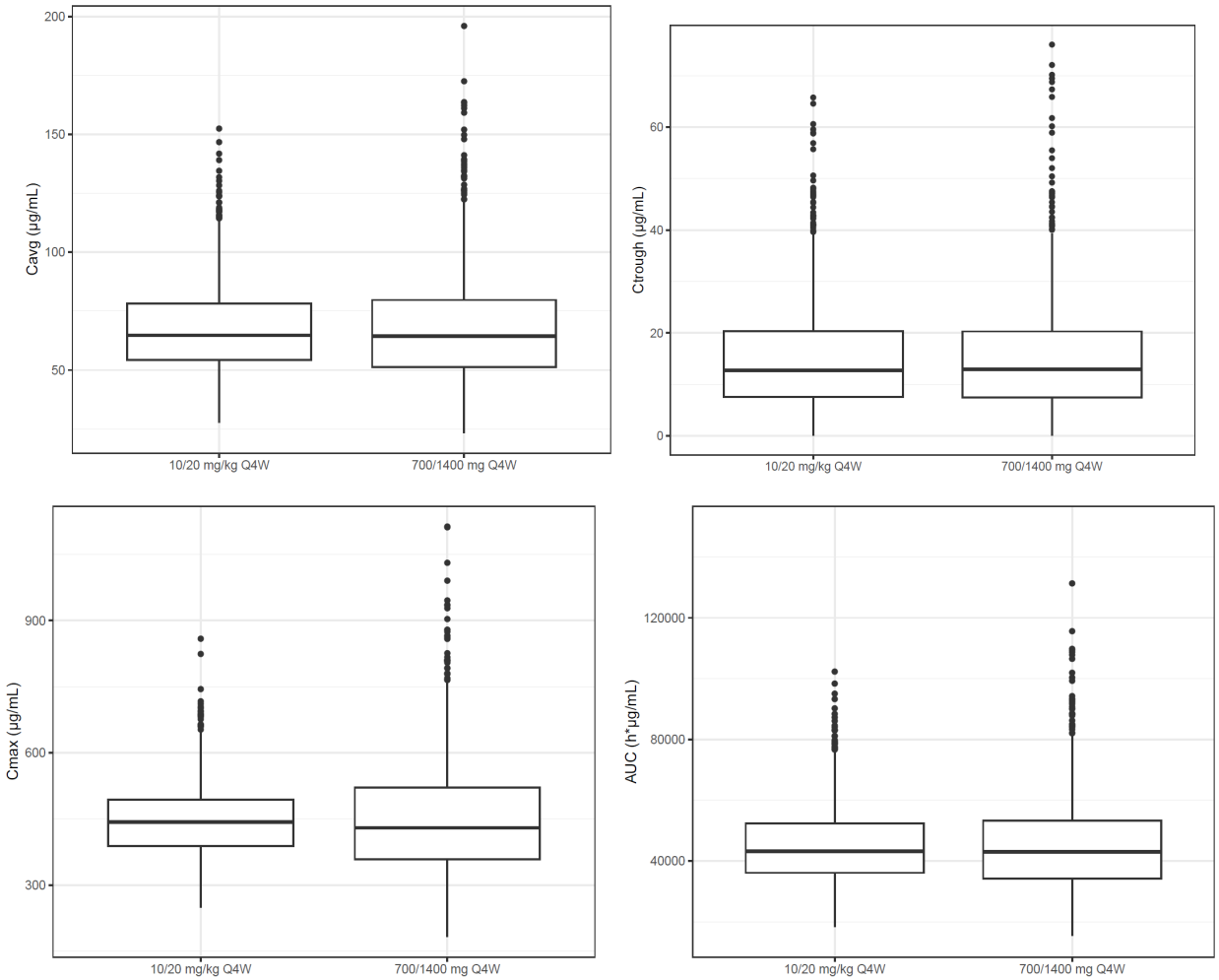
Body weight was identified as a significant covariate on total body and distributional clearances, as well as central and peripheral volumes of distribution. Body weight increases clearance and volume of distribution following typical allometric relationships (exponent of 0.8 for clearance terms and exponent of one for volume terms). Accordingly, heavier patients are expected to have higher clearance and higher volume of distribution, resulting in lower overall exposure (Figure 5). Changing from weight-based (in Study AACD) to flat dosing (Studies AACG, AACH and AACI) as shown through PK simulations, resulted in modest increase in Cmax,ss variability, but no meaningful changes in AUCss or trough concentrations at steady state (Figure 3).

Figure 2. Simulated relationship between PK and body weight at steady state (1400 mg Q4W)



Abbreviation: Q4W = every 4 weeks.
Solid line represents median predicted concentration-time profile. Shaded regions represent 90% prediction intervals.

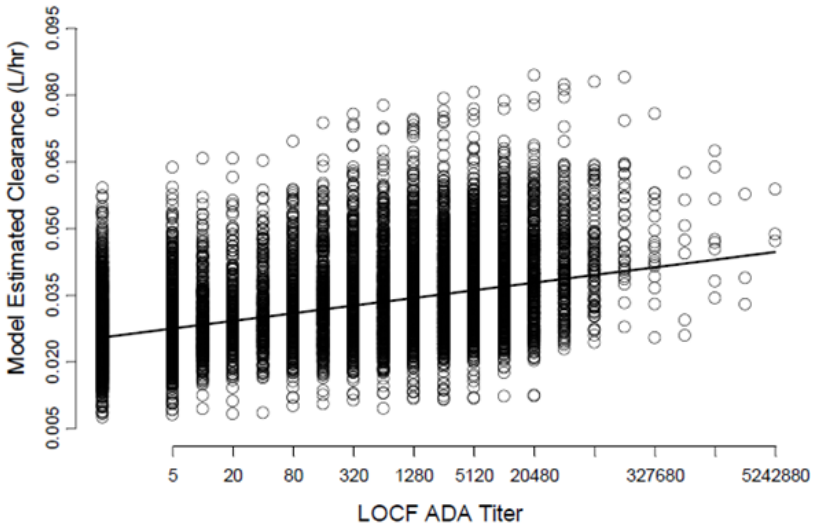
Figure 3. Body weight impact using simulations with the final popPK model for Cavg, Cmax, Ctrough, and AUC at steady state



Abbreviations: AUC = area under the concentration versus time curve; AUC_{ss} = area under the concentration versus time curve at steady state; C_{avg} = average drug concentration; $C_{av,ss}$ = average drug concentration under steady state conditions during multiple dosing; C_{max} = maximum observed drug concentration; $C_{max,ss}$ = maximum observed drug concentration at stead state; C_{trough} = drug concentration before the next dose; PK = pharmacokinetic; Q4W = every 4 weeks.
Note: lower and upper hinges correspond to 25th and 75th percentiles; The upper whisker extends from the hinge to the largest value no further than 1.5 * inter-quartile range.

Based on the population PK analyses, donanemab clearance increased proportionally to the logarithm of ADA titre (Figure 4). To evaluate titre impact, PK parameters were calculated for ADA- and each titre category using simulations with 3000 virtual participants. Specifically, estimated median, 5th, 20th, 80th, and 95th percentiles for trough concentrations, AUC, average drug concentration (Cav) and Cmax at steady state for different titre cut-offs as well as ADA-negative status, are reported in Table 4.

Figure 4. Proportional increase in donanemab model-estimated clearance with ADA titre increase



Abbreviations: ADA = antidrug antibody; LOCF = last observation carried forward.

Table 4. steady state exposures according to ADA status and titre

	Median (90% CI): 50th (5th-95th Percentiles)			
ADA status/titer category	**$AUC_{\tau,ss}$**	**$C_{average,ss}$**	**$C_{max,ss}$**	**$C_{trough,ss}$**
units	[µg*h/mL]	[µg/mL]	[µg/mL]	[µg/mL]
ADA negative	53500 (34900, 91500)	79.6 (52.0, 136)	381 (255, 559)	22.2 (5.63, 55.3)
<1:5120	43700 (26200, 76100)	65 (38.9, 113)	358 (232, 558)	13.6 (3.04, 37.6)
1:5120-1:20480	37800 (23500, 63000)	56.3 (35, 93.7)	350 (231, 561)	10.0 (1.87, 25.6)
>1:20480	36300 (22300, 69200)	54 (33.1, 103)	350 (224, 565)	9.33 (1.47, 28.3)
	Median (60% CI): 50th (20th-80th Percentiles)			
ADA negative	53500 (42600, 68500)	79.6 (63.3, 102)	381 (307, 454)	22.2 (11.6, 33.6)
<1:5120	43700 (33600, 58500)	65 (50.0, 87.1)	358 (286, 449)	13.6 (7.05, 23.9)
1:5120-1:20480	37800 (29600, 48800)	56.3 (44.1, 72.6)	350 (279, 440)	10.0 (5.11,17.0)
>1:20480	36300 (28500, 50100)	54 (42.4, 74.6)	350 (274, 437)	9.33 (4.58, 16.4)

Abbreviations: ADA = antidrug antibody; $AUC_{\tau,ss}$ = area under the concentration versus time curve during 1 dosing interval at steady state; $C_{average,ss}$ = average drug concentration under steady-state conditions during multiple dosing; CI = confidence interval; $C_{max,ss}$ = maximum observed drug concentration during a dosing interval at steady state; $C_{trough,ss}$ = minimum observed drug concentration during a dosing interval at steady state; TE ADA = treatment-emergent antidrug antibody.

Pharmacokinetic interaction studies

DDIs are unlikely, as donanemab is an antibody that is not metabolized by hepatic cytochrome P450 enzymes.

2.6.2.2. Pharmacodynamics

Mechanism of action

Donanemab is a humanized immunoglobulin gamma 1 (IgG1) monoclonal antibody derived from the parental murine surrogate mE8 and was developed as a human IgG1 isotype to maximize the effector function in humans. Donanemab is directed against insoluble, modified, N terminal truncated form of amyloid beta (N3pG Aβ) present only in deposited brain amyloid plaques of AD patients.

Non-clinical studies found that donanemab binds to N3pG Aβ with high affinity (<1 nM), while it did not recognize the soluble human Aβ1-40 or Aβ1-42 peptide. Previous studies have suggested that anti-Aβ therapeutic antibody binding to soluble forms of Aβ in the CNS may result in poor recognition of deposited Aβ (target engagement) due to antibody saturation with soluble monomer (DeMattos et al. 2012). In contrast, an antibody specific for deposited plaque is hypothesized to have increased target recognition and plaque lowering ability. Ex vivo studies demonstrated that donanemab and the murine surrogate mE8c can bind and lead to the microglial phagocytosis of deposited amyloid plaque.

Primary and Secondary pharmacology

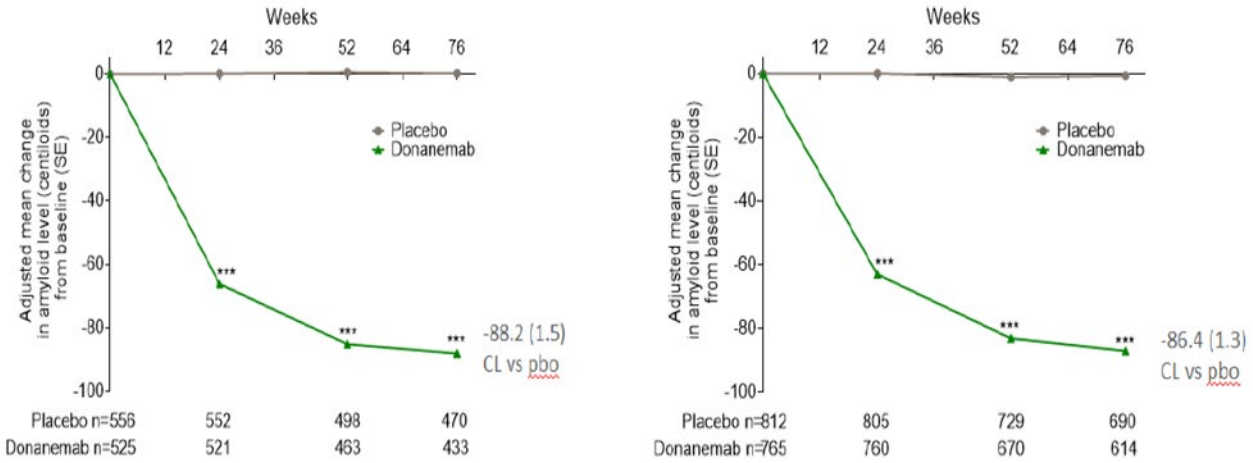
The target PD activity of donanemab is to reduce amyloid plaque. Amyloid plaque load was assessed by F-18 florbetapir PET scans. Analyses of the florbetapir PET scans were performed according to a Standardized Uptake Value ratio (SUVr) method (Clark et al. 2011; Joshi et al. 2015). A SUVr threshold of 1.10 was used to discriminate between amyloid positive and amyloid-negative patients. The SUVr values were converted to Centiloid units (Navitsky et al. 2018). A threshold of less than 24.1 Centiloids on amyloid PET is considered by the applicant to represent clearance of amyloid (also referred to as amyloid-negative) (Navitsky et al. 2018).

In studies AACD (phase 1b), AACG (phase 2) and AACI (phase 3), the effect of donanemab on cerebral amyloid load was evaluated. In all three studies, a reduction in amyloid beta load after donanemab treatment is observed in the phase 1b, 2 and 3 studies.

Reduction in amyloid plaque among participants receiving 3 to 5 doses of 10 mg/kg donanemab was observed. The participants who received 10 mg/kg IV had a mean Centiloid change of -47.6 (standard deviation: 13.5), compared with minimal change in the pooled placebo groups, corresponding to a mean 40% to 50% reduction of brain amyloid. The significant reductions in amyloid plaque level compared with placebo were observed with donanemab at the first assessment (12 weeks) and were sustained up to 72 weeks. 20 mg/kg Q4W achieved greater reduction in amyloid plaque at most time points compared with either 10 mg/kg Q2W or 10 mg/kg Q4W.

Patients in study AACI were according to their cerebral tau load included in the intermediate population (low-medium load) or in the overall population (low, medium and high tau). Figure 8 shows the change in amyloid levels in the phase 3 study. A proportion of donanemab-treated patients (34% and 30%) had amyloid plaque clearance (<24.1 CL) at six months in the intermediate tau and overall populations, respectively. A total of 80% of donanemab-treated patients in intermediate tau population and 76% in the overall population had clearance at 18 months.

Figure 5. MMRM: Change in amyloid level (Centiloid units, CL) from baseline to Week 76 (AACI-PC period), intermediate population (left panel) and overall population (right panel).

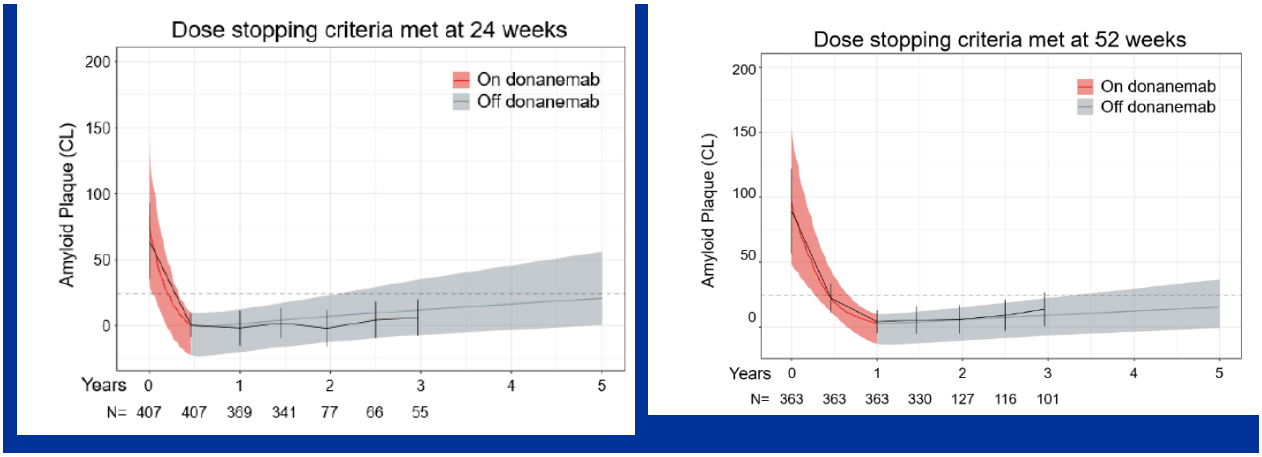


Abbreviations: CL = Centiloid; LS = least squares; MMRM = Mixed Model for Repeated Measures; pbo = placebo; PC = placebo-controlled; SE = standard error. **** p<.0001.

The impact of discontinuing active treatment on plaque re-accumulation was investigated by simulations using treatment exposure-response (amyloid plaque) model using previously published methods (Shcherbinin et al. 2022; Gueorguieva et al. 2023). The amyloid re-accumulation rate (median, 95% CI) is estimated at 2.80 (2.16, 3.11) Centiloids/year. This finding is supported by natural accumulation modelling studies (Jagust et al. 2021), showing approximately 3.3 Centiloids/year estimated rate of the natural amyloid accumulation model. In the group of participants who achieved amyloid plaque levels below 11 Centiloids by 6 months (from Studies AACG and AACI), completion of active donanemab treatment did not result in a substantial increase in amyloid PET signal through to 1.5 years (end of Studies AACG and AACI) and further to approximately 3 years.

Late in the procedure, the applicant submitted data on re-accumulation from the LTE phase of AACI trial (see Figure 6 below).

Figure 6. Participants completing active donanemab treatment at 24 weeks and at 52 weeks.



Study AACI included the following exploratory plasma biomarkers: p-tau217, P-tau181, glial fibrillary acidic protein (GFAP) and neurofilament light chain (NfL). In addition, brain tau deposition (PET scan), volumetric MRI. Flortaucipir F18 PET provides quantitative assessment of tau deposition in the brain and can serve as a PD biomarker of accumulation of tau deposits as AD progresses. Volumetric MRI is included to assess the effect of donanemab versus placebo on brain tau deposition.

Brain tau deposition

In the intermediate tau population, the ANCOVA showed that change from baseline to Week 76 in tau deposition did not differ between the donanemab group and the placebo group; ANCOVA (evaluable efficacy set) LS mean change difference (95%CI) = -0.002 (-0.02, 0.01; p=.84). Similar results were observed in the overall population (p=.38)

Volumetric MRI

Donanemab-treated intermediate tau patients had greater reduction in bilateral whole brain volume than placebo-treated patients at week 76; MMRM (evaluable efficacy set) LS mean change difference ± SE was -6.33 ± 0.63 cm3 (p=<.001). Comparable results were found in the overall population: LS mean change difference ± SE was -6.66 ± 0.56 cm3 (p=<.001).

P-tau217

In the intermediate tau population, the change from baseline plasma P-tau217 level was reduced in donanemab-treated patients and increased in placebo-treated patients at Week 76. Change from baseline at week 76: MMRM (evaluable efficacy set) LS mean change difference (95%CI) = -0.25 (-0.28, -.022; p<.0001). Similar decrease in the P-tau217 level in the donanemab group and increase in the placebo group were observed for overall population at week 76 (p<.0001).

P-tau181

In the intermediate tau population, the change from baseline plasma P-tau181 level was reduced in donanemab-treated patients and increased in placebo-treated patients at Week 76. Change from baseline at week 76: MMRM (evaluable efficacy set) LS mean change difference (95%CI) = -0.10 (-0.12, -.09; p<.0001). Similar decrease in the P-tau217 level in the donanemab group and increase in the placebo group were observed for overall population at week 76 (p<.0001).

GFAP

In the intermediate tau population, plasma GFAP level was reduced in donanemab-treated patients and increased in placebo-treated patients at Week 76. Change from baseline at week 76: MMRM (evaluable efficacy set) LS mean change difference (95%CI) = -0.14 (-0.16, -.12; nominal p<.001). At Week 76, difference in LS mean change values between the donanemab and placebo groups was observed in the overall population.

NfL

In the intermediate tau population, plasma NfL levels were comparable between donanemab-treated patients and placebo-treated patients at Week 76. Change from baseline at week 76: MMRM (evaluable efficacy set) LS mean change difference (95%CI) = -0.01 (-0.03, 0.01; nominal p<.15). At Week 76, also no difference in LS mean change values between the donanemab and placebo groups was observed in the overall population.

APOE ε4 carrier status - ARIA

The effect of APOE ε4 carrier status on ARIA-E (based on MRI and TEAE cluster) was evaluated given its known association with ARIA. APOE ε4 carrier status was associated with increased frequency of ARIA events (Population PK/PD report). Results from a post hoc ARIA risk factor analysis showed APOE ε4 genotype was associated with ARIA-E, symptomatic ARIA-E, and ARIA-H.

Plasma concentration – ARIA

There was a clear donanemab treatment effect on baseline hazard of ARIA-E (based on MRI or TEAE cluster). In addition, the average concentration donanemab at steady state (Cav,ss) was a significant risk factor increasing the baseline hazard for individuals on donanemab. The risk for ARIA-E was 1.2 times higher in participants with the highest observed Cav,ss (233 µg/mL, 0.05% of the PK evaluable population) compared with those with median Cav,ss (52.1 µg/mL, 50% of the PK evaluable population).

ADA – infusion related reactions

Among 984 donanemab-treated participants, 82 (8.3%) reported a preferred term (PT) of infusion related reaction on the day of infusion. According to the titre group, the distribution of participants reporting this PT is: 46 of 140 (32.9%) in the upper titre group, constituting 56.1% of the 82 participants who reported an infusion related reaction; 25 of 350 (7.1%) in the middle titre group, constituting 30.5% of the 82 participants who reported an infusion related reaction; and 11 of 487 (2.3%) in the lower titre group, constituting 13.4% of the 82 participants who reported an infusion related reaction.

2.6.3. Discussion on clinical pharmacology

Donanemab has been administered in four completed clinical studies: I5T-MC-AAC (AACC, phase I), I5T-MC-AACD (AACD, phase I), I5T-MC-AACG (AACG, phase II), and the placebo-controlled part of I5T-MC-AACI (AACI-PC, phase III). Ongoing studies include Part B of Study I5T-MC-AACH (AACH, phase II), the long-term extension study period of Study I5T-MC-AACI (AACI-LTE, phase III), and Safety Addendum of Study I5T-MC-AACI (AACI-Safety Addendum, phase III).

The pharmacokinetic data provided are sufficient to describe the PK of donanemab. Several doses have been tested (single dose and multiple dose) in patients, and sufficient PK data are also obtained (in the phase III study) for the dose proposed in the SmPC. In addition, PK samples were analysed in a popPK analysis. In this analysis, PK data from study AACH and AACI-safety addendum were already included. The popPK dataset contained 22,288 observations from 2131 participants (46 participants from Study AACD, 131 participants from Study AACG, 54 participants from Study AACH, Part B, and 1900 participants from AACI [PC and Safety Addendum]).

Analytical methods

Detection of donanemab in human serum was performed using an ELISA assay. In general, this bioanalytical method validation was acceptable and in line with current requirements/guidelines. Incurred sample analysis was reported and within limits as defined in ICH M10. Accuracy and precision in the study reports were largely similar compared to values reported in the method validation report. Missing reports (bioanalytical reports for study AACC and interim bioanalytical report for study AACH [study ongoing]) were provided in the second round of assessment and were acceptable.

ADA effects on donanemab recovery were detected at 3000 ng/mL, but not 30000 ng/mL. 3000 ng/mL is not below trough concentrations reported. An effect of ADA on PK was also described in the popPK model (see below). The applicant was requested to substantiate how the lack of assay drug tolerance

could impact characterisation of donanemab PK in the first round of assessment. The applicant supported that the majority of the antibodies are neutralizing. The bioanalytical assay therefore quantifies only active donanemab with at least one β-amyloid binding site. This is indeed considered the relevant pool of circulating donanemab. According to the ELISA validated methods (8352-532, 8338-154, 8352-531, 8248-152), the longest approved long-term storage duration was 211 days at temperatures between -60 to -80°C and up to 83 days at -15 to -30°C. For samples analyzed in support of clinical studies I5T-MC-AACC, I5T-MC-AACD, I5T-MC-AACG, and I5T-MC-AACI, the storage durations were 364 days, 596 days, 623 days, and 501 days, respectively. The applicant provided the missing long-term stability results (stability up to 631 days) in the second round of assessment.

For CSF samples, initially only raw data are available for LY3002813 determination. The applicant was invited to submit bioanalytical result performed during clinical studies AACC and AACD in CSF. Data was provided supporting that donanemab geometric mean ratio between serum and CSF (Study AACC only) is 0.001711, which has also been reported for other antibodies**.**

PopPK

PopPK modelling and simulations analysis were performed on the combined data derived from clinical studies I5T-MC-AACD, I5TMC- AACG, I5T-MC-AACH (Parts B and C), and I5T-MC-AACI (PC and Safety Addendum). The results of the I5T-MCAACH study could not be identified in the dossier. The only information initially provided is that this study is still ongoing. The applicant indicated what results from this study were used in the modelling (i.e. 54 participants from part B for serum donanemab, 15 participants part C to analyse exposure to amyloid plaque).

In general the strategy chosen for the popPK analysis is considered acceptable. Model simulations are performed for the population from which the data has been gathered. Percentage of measured samples below LLOQ is high, therefore the choice for the M3 method is considered suitable. The pharmacometrics analysis plan was followed. A two-compartment model is a reasonable choice based on the shape of the PK data provided. During covariate selection the additional covariates "study" and "formulation" were also tested. Parameters were estimated with sufficient precision and shrinkage values reported are acceptable. Generally, the VPCs are also acceptable, although slight overprediction at later time points after dosing is observed (>15 weeks after dose), which may point towards a slightly underestimated clearance. Unexplained variability in the model is high. Next to weight, only the titre effect was identified as a significant covariate. Multiple diagnostic plots were provided to further confirm that the model was acceptable in the second round of assessment.

Multiple PK-PD models were described by the applicant (for more information, see clinical AR). Direct treatment effect models were generally superior over models that used change in amyloid for mediation of clinical effects, and were used for the PK-amyloid, PK-Ptau217, PK-IADRS and PK-CDRSB relationships. In the PK-PD models no concentration-dependent effects were considered. Although this is atypical, the explanation by the applicant that this is most likely due to the use of only a single dose regimen in the (majority of the) clinical studies is considered plausible. The choice made during the modelling are described only to a limited extent. In general, the model development resulted, however, in reasonably precise parameter estimates and the model predictions were in line with measured data, as shown in the VPCs. The models are considered sufficient for description of the measured data and for the analysis of potential covariate effects. However, the impact of standard Alzheimer's disease treatments, including ACHE inhibitors and memantine, on the efficacy and safety profile of donanemab treatment, particularly concerning the incidence of ARIAE, still needed to be analyzed by the applicant after the first round of assessment. It was later concluded that donanemab exhibited a similar effect in slowing disease progression for participants both on and not on concurrent AD medication.

One inconsistency identified in the amyloid plaque model is that simulations did not capture the effect of ADA titre on amyloid plaque reduction, which was identified clinically ("the lower and middle titre categories show a greater impact of donanemab on amyloid plaque reduction than the upper titre categories, all titre categories show significant separation from placebo"). The clinical data are therefore considered pivotal.

In addition to describing the data, the IADRS and CDR-SB models were used for extrapolation beyond the treatment period in the clinical studies (i.e., five year simulations), assuming linear disease progression rate. According to the applicant this could indicate that disease slowing increases over time, however, as this assumption is not supported by any (mechanistic) rationale/data and is therefore uncertain, this extrapolation is considered only hypothetical and extrapolated model outcomes will not be considered in the B/R analysis.

Bioequivalence

Two different formulations were used during clinical development: the liquid formulation and the lyophilized formulation, with the liquid formulation being the proposed commercial formulation. No formal bioequivalence or bioavailability study has been conducted, although formulation was tested as covariate in the popPK model. Nevertheless, the applicant was asked to make an effort to construct bioequivalence data from available PK data (Cmax, AUC and Tmax), from studies using the liquid formulation and the lyophilized formulation, and describe the ratios of these parameters between the liquid and the lyophilized formulation. In addition, pcVPCs for donanemab concentrations stratified on formulation type (lyophilized form and liquid form) were requested. Based on these PK data provided by the applicant in the second round of assessment, differences in exposure between the two formulations are not expected.

ADME

Distribution.

The observed CSF to serum concentration ratio was approximately 0.00208 (0.208%) across all participants and dose levels. This value is now included in the SmPC.

In the study I5T-MC-AACD, it was observed that following single doses of donanemab the volume of distribution decreased (by approximately 30% for the 40 mg dose compared to the 10 mg dose). In the case of multiple dosing, the volume of distribution was approximately half as much as with single dosing (single dose 40 mg – 6.36L vs. 20 mg Q4W – 3.66L). The applicant indicated that the reason of reduction of volume of distribution with increasing dose was the small sample size, which is acceptable.

Dose proportionality and time dependency.

Cmax and AUC are approximately dose-proportional for doses above 10 mg/kg. The AUC0-inf was not to be dose proportional for doses that are below 10 mg/kg. However, as concentration at multiple time points is below LLOQ, the distribution phase could be affecting the terminal slope and therefore calculated half-life. This possibly could result in an underestimation of these PK parameters. Therefore, a statement on dose proportionality is now included in the SmPC for the dose range 700 mg up until 1400 mg.

Further, it is agreed that no pronounced time-dependency is observed in the phase I study. The accumulation rates reported are roughly in line with what is expected based on the reported half-life and dosing interval. The applicant further substantiated that also ADA titre will not result in time dependent effects on PK in the second round of assessment. Absence of a time dependency is also sufficiently described in the SmPC for the dose range 700 mg up until 1400 mg.

Special populations

Age, gender, race, renal function, hepatic function and APOE ε4 carrier status were all evaluated as potential covariates in the popPK analysis. No effects on PK where detected. Lack of effect has been described in SmPC section 5.2. In addition, the applicant summarised PK parameters per hepatic- and renal-impairment category, due to the low number of patients in the more severely affected groups. Exposure does not appear to change per hepatic function category. However, a difference of exposure with renal function status appears to be present. This was not identified as a covariate in the popPK model. The applicant justified absence of clinically relevant effects of renal impairment on efficacy/safety, based on exposure-efficacy/safety relationships.

Body weight was identified as a significant covariate on total body and distributional clearances, as well as central and peripheral volumes of distribution. Changing from body weight-based dosing to flat dosing appears not to have large effects on mean AUC and Ctrough values. In addition, variance in reported AUC and Ctrough is comparable. The applicant was requested to explain the (average) increase in Cmax value when flat dosing is used (Figure 6), as the dose for an average individual of ~70kg did not change (20mg/kg v.s. 1400 mg), and distribution volumes scale linearly with body weight. The applicant indicated that this was due to a coding error in the second round of assessment, which is an acceptable explanation. In addition, the applicant provided a comparison for Cav,ss between body weight based and flat dosing, as Cav,ss influences ARIA-E risk. Cav,ss was very similar between body weight based and flat dosing.

In patients with the highest body weight and the highest ADA antibody titres, a substantial reduction in drug exposure can be expected. Furthermore, the conducted analyses do not indicate any advantage of using a fixed dose overweight-based dosing. In the second round, the applicant provided additional justification for the flat dosing recommendation. Transitioning from weight-based to flat dosing led to a slight increase in variability in Cmax,ss, but did not significantly alter AUCt,ss, Cav,ss, or Ctrough concentrations. Given that none of the parameters associated with an optimal benefit-to-risk ratio depended on achieving lower variability in Cmax,ss, further optimisation of the therapeutic range through body weight-based dosing was deemed unnecessary.

An effect of ADA titre on PK was identified by the applicant. High titre values result in a significant reduction in predicted exposure. This is now reflected in SmPC section 5.2.

Lastly, Table 5 shows the number of participants in the population PK model by age and by study.

Table 5. Number of participants (%) included in the population PK model, segregated by age groups and studies

	Age 65-74 (Older Participants Number / Total Number)	**Age 75-84 (Older Participants Number / Total Number)**	**Age 85+ (Older Participants Number / Total Number)**
All studies (n = 2131)	910 (43%)	1002 (47%)	53 (2%)
AACD (n = 46)	19 (2%)	15 (2%)	5 (9%)
AACG (n = 131)	55 (6%)	66 (7%)	5 (9%)
AACH (n = 54)	15 (2%)	34 (3%)	5 (9%)
AACI (n = 1900)	821 (90%)	887 (88%)	38 (72%)

Abbreviations: n = number of participants; PK = pharmacokinetic.
Note: Approximately 8% of all participants were less than 65 years old.

Pharmacodynamics

In the pivotal study, two amyloid PET tracers were used; 18F-florbetapir and 18F-florbetaben. In the majority of patients 18F-florbetapir was used as tracer. A SUVr threshold of 1.10, equivalent to 24.1 centiloids, was used to classify amyloid-negative from amyloid-positive subjects for study inclusion. Because these two tracers have different SUVr values, the values were converted into centiloids. At baseline, cerebral amyloid load was expressed in centiloids with all patients having a mean centiloid of 100 or slightly above. A reduction in cerebral amyloid load, expressed in centiloids, was observed after donanemab treatment as compared to placebo. In addition, baseline values and data of SUVR change in six cortical regions (anterior cingulate, posterior cingulate, parietal, precuneus, temporal, medial orbitofrontal) are provided for the placebo- and donanemab groups in low-medium tau, high tau, and combined populations. At baseline, SUVR values were comparable between groups with the largest accumulation in the anterior cingulate and precuneus. A difference in amyloid reduction between placebo and donanemab in SUVR is visible in the three subgroups for each cortical region, with most amyloid reduction in the anterior cingulate and precuneus.

No difference between placebo and donanemab was found in brain tau deposition after 76 weeks of treatment. This is in contrast to the p-tau findings in plasma. It could be the result of different aspects of tau pathology as reflected by plasma P-tau217 and Tau PET.

The applicant quantified the effect of the covariate "donanemab treatment" on ARIA-E hazard. The baseline hazard was 12.2 times higher for APOE4 heterozygotes on treatment compared with those on placebo.

The APOE ε4 carrier status is not identified as a significant factor in the amyloid PET model, as the risk of the AD is much higher in the group that has got two copies of E4, the applicant was asked to present the analysis separately for the E4/E4 and E3/E4 genotype. Results suggested that the clearance of amyloid plaques is independent of the APOE4 genotype.

2.6.4. Conclusions on clinical pharmacology

In general, PK was investigated to a reasonable extent and no questions remain.

The effect on cerebral Aβ load as measured by the PET scan consistently confirm the effect of donanemab on the Aβ pathophysiology of AD. Target engagement of Aβ and proof of concept is considered established. The re-accumulation rate of amyloid is estimated at 2.4 centiloids/year. Exploratory data suggest that at week 76, p-tau217, p-tau181 and GFAP were decreased after donanemab treatment compared to placebo. This might imply an effect of donanemab on the downstream tau-related biomarkers, which would reflect the supposed causal pathophysiology of AD. However, on tau PET readouts no differences between donanemab and placebo were seen. One explanation is that that plasma P-tau and Tau PET might reflect different aspects of tau pathology. In addition, donanemab is associated with greater reductions in whole brain volume. Also, donanemab is associated with an increased risk of ARIA, with ε4 homozygotes having a significant higher risk of ARIA compared to ε4 non-carriers. Furthermore, more patients with high ADA titres have injection-related reactions (IRR) than patients with lower ADA titres.

2.6.5. Clinical efficacy

Introduction

Study AACI is presented as the pivotal study for efficacy of donanemab to slow disease progression in symptomatic adult patients with Alzheimer's disease (AD) with evidence of amyloid beta pathology and

a clinical diagnosis of either mild cognitive impairment due to AD or mild AD dementia. Study AACG is submitted as supportive. In addition, Study AACN is ongoing. This is an active comparator study of donanemab and aducanumab. As no efficacy data are available yet this study is not discussed.

Scientific advice

In the 2021 advice, the CHMP expressed the need for a well-designed randomised clinical trial that establishes a clear relationship between amyloid reduction and clinical outcome, expressing that this had not been established in the Phase 2 Study AACG. Although there was no strict objection to the iADRS as a primary endpoint, the CDR-SB was considered the preferred primary endpoint. In addition, CHMP raised concerns about the primary analysis by Bayesian disease progression model, recommending the use of MMRM. In Study AACI, iADRS is the primary endpoint assessed using NCS2 analysis, and CDR-SB was pre-specified as a key secondary endpoint assessed using MMRM.

In addition, as the patients in the study are defined by amyloid and tau status it was considered likely that this will be reflected in the indication since it also defines the target population.

In the 2022 follow-up advice, the CHMP expressed that the extrapolation of efficacy to a target population defined by current CSF and blood tests would need thorough justification at the time of MAA, and that specificity and sensitivity of defining the target population by CSF test instead of PET needed to be calculated from external studies.

Finally, CHMP acknowledged that a treat-to-target approach is considered well justified but that some patients may not be suitable or willing to conduct efficacy follow-up examinations requiring PET or CSF. Therefore, treatment cessation or defining a maximum duration for treatment could be appropriate to be included in future labelling.

2.6.5.1. Dose response study(ies)

Before Study AACG, prior exposures had included 0.1, 0.3, 1, 3, 10, 20, and 40 mg/kg in single and/or multidose dosing schedules. The highest dose of donanemab tested in humans is 40 mg/kg, administered as a single dose in Study AACD (for context, this is equivalent to 2800 mg in a 70-kg individual). Because two of the four participants who received a single 40-mg/kg dose developed ARIA-E, and given that ARIA is related to total dose received, it was presumed that multiple dosing of 40 mg/kg would result in higher ARIA rates than observed with single dosing. Thus, assessment of multiple dosing in Study AACD was limited to a total monthly dose of 20 mg/kg (that is, 10 mg/kg every two weeks or 20 mg/kg every four weeks). Both of these dosing regimens had lower rates of ARIA-E.

Data from Study AACC and AACD suggested that PK of LY3002813 is linear when the dose is not less than 10 mg/kg. Mean half-life was about nine-11 days when dose is ≥ 10 mg/kg, so minimal accumulation in plasma PK was predicted for 700 mg and 1400 mg Q4 week IV dosing. High levels of 18F florbetapir PET signal reductions were seen with a single dose of 20mg/kg, and are comparable to 18F florbetapir PET reductions seen with a 10 mg/kg Q2 week dosing schedule at three months. Based on this as well as decreased patient burden with an every four week dosing schedule compared with an every two week dosing schedule and comparable safety, 1400 mg Q4 week dosing was selected as the highest dose regimen for robust amyloid plaque lowering.

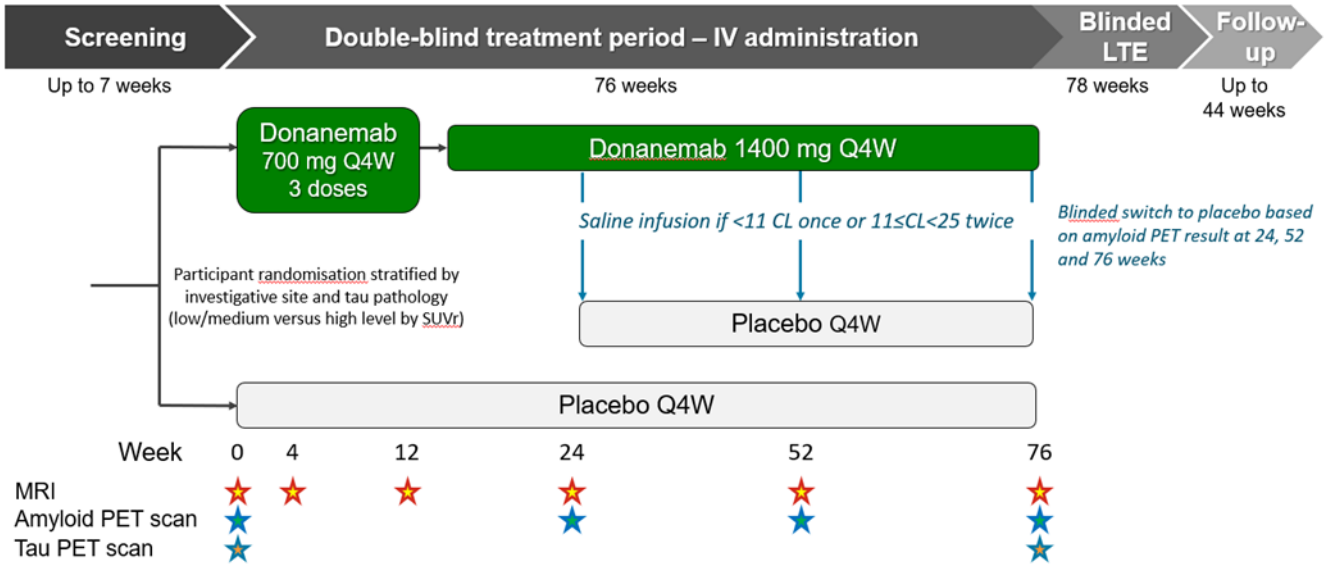
2.6.5.2. Main study

Study AACI

Methods

Study I5T-MC-AACI (Study AACI) was a randomized, parallel-group, double-blind placebo-controlled phase III study in patients with Mild Cognitive Impairment (MCI) and Mild Alzheimer's disease (AD). Figure 7 shows the design of Study AACI.

Figure 7. Study design – Study AACI



Abbreviations: CL = Centiloid unit; IV = intravenous; LTE = long-term extension; MRI = magnetic resonance imaging; PET = positron emission tomography; Q4W = every 4 weeks; SUVr = standardised uptake value ratio.
Figure obtained from slides of pre-submission meeting with applicant (16 June 2023).

Study Participants

Main Inclusion criteria were:

- Age between 60 and 85 years.
- Gradual and progressive change in memory function reported by the participant or informant for 6 months or more.
- MMSE score of 20 to 28 (inclusive).
- Evidence of tau deposition as observed by flortaucipir F 18 PET scan.
- Evidence of amyloid beta deposition as observed by florbetapir F 18 or florbetaben F 18 PET scan.
- A study partner who will provide written informed consent to participate, is in frequent contact with the participant (defined as at least 10 hours per week), and will accompany the participant to study visits or be available by telephone at designated times.

Main Exclusion criteria were:

- Any contraindications for MRI or PET.
- Presence of ARIA-E, greater than 4 cerebral microhaemorrhages, more than 1 area of superficial siderosis, any macrohaemorrhage or severe white matter disease at screening (centrally read MRI).
- Sensitivity to florbetapir F 18 or florbetaben F 18 or flortaucipir F 18.

Concomitant allowed medication

Use of approved or standard of care symptomatic treatments for AD is permitted during the study, provided that the dose has been unchanged for 1 month before Visit 2. Doses of these medications should remain constant when possible throughout the double-blind period (Visit 2 to Visit 21). Concurrent use of passive anti-amyloid immunotherapies other than donanemab, such as gantenerumab, lecanemab, or aducanumab, was not permitted during the study.

Nonmedication treatments for AD such as behavioural management are permitted but are subject to the same restrictions as medication treatment taken for AD. Vaccinations and medications to manage infusion reactions are allowed during the study. Not allowed was immunoglobulin G (IgG) therapy.

Treatments

Randomised patients received either placebo (saline) or donanemab. Both were administered by IV infusion every 4 weeks (Q4W). The first 3 doses of donanemab were 700mg followed by 1400mg.

Dose cessation criteria

Donanemab-treated participants could switch to placebo in a blinded manner during the study if they met either 1 of the 2 criteria at Week 24, 52, or 76:

1. amyloid level was <11 CL at any single amyloid PET scan, or

2. amyloid level was ≥11 to <25 CL in 2 consecutive amyloid PET scans.

Dose modification in case of ARIA

For participants who developed ARIA during the titration period (that is, before the fourth infusion of study drug of the AACI-PC period or of the extension period), the investigator could decide to

• temporarily suspend dosing, then determine if the participant needed to remain on the pre-suspension dose (700 mg/placebo equivalent) either temporarily beyond the first 3 doses or throughout the remainder of the treatment period

• continue the same dose (700 mg/placebo equivalent) either temporarily beyond the first 3 doses or throughout the remainder of the treatment period.

Objectives

The primary objective and some of the secondary objectives were to evaluate the efficacy of donanemab versus placebo on clinical progression in patients with early symptomatic AD.

The secondary objectives were to assess the effect of donanemab versus placebo on: 1) clinical progression in patients with early symptomatic AD, 2) brain amyloid deposition, 3) brain tau deposition, 4) brain region volumes. In addition, the safety and tolerability of donanemab was evaluated and the peripheral PK and presence of anti-donanemab antibodies was evaluated.

The exploratory objectives were to assess:

- the probability of amyloid clearance in the donanemab group versus placebo.

- the effect of donanemab versus placebo on: 1) time progression of the disease in participants with early symptomatic AD, 2) the difference in hazard of progressing to first meaningful clinical worsening event, 3) the probability of non-progression at Week 52, and 4) blood-based biomarkers.

Outcomes/endpoints

Primary endpoint:

- Change from baseline in iADRS score at Week 76*.

Secondary endpoints:

- Change from baseline in CDR-SB, ADAS-Cog13, ADCS-iADL, MMSE scores at Week 76*.
- Change from baseline in brain amyloid plaque deposition as measured by florbetapir F18 PET at Week 76.
- Change from baseline in brain tau deposition as measured by flortaucipir F18 PET at Week 76.
- Change from baseline in volumetric MRI measures at Week 76.
- Incidence of all AEs and SAEs.
- Brain MRI findings, including incidence of ARIA-E and ARIA-H
- Infusion-related reactions
- Incidence of anti-donanemab antibodies in serum

Most important tertiary endpoints:

- Slowing in time progression measured by iADRS and CDR-SB
- Progression in first meaningful clinical worsening (predefined on iADRS and CDR-SB)
- No progression = less or equal to 0 on CDR-SB
- Plasma NfL, GFAP, P-tau and ABeta levels.

* in at least one of these populations; the intermediate tau population or the overall population.

Integrated Alzheimer's Disease Rating Scale - (iADRS)

The integrated Alzheimer's Disease Rating Scale (iADRS) (Wessels et al. 2015) represents a composite that was developed using both a theory-driven approach (incorporating measures of both cognition and function) and a data-mining approach (identifying the most sensitive combination of scales through analysis of data from the Alzheimer's Disease Neuroimaging Initiative and the EXPEDITION, EXPEDITION2, and EXPEDITION3 studies). The applicant developed and validated the iADRS and its utility as a primary endpoint.

The iADRS is a simple linear combination of scores from 2 well-established, therapeutically sensitive, widely accepted measures in AD, the ADAS-Cog13 and the Alzheimer's Disease Cooperative Study – instrumental Activities of Daily Living (ADCS-iADL), measuring the core domains of AD. All items of these 2 scales are included without additional weighting of items, yielding face validity and ease of interpretation of the composite relative to its components. The iADRS score (maximum 144 points) will

be derived from the ADAS-Cog13 (maximum 85 points) and the ADCS-iADL (maximum 59 points). The ADAS-Cog13 and the ADCS-ADL will be the actual scales administered to patients.

The iADRS captures clinical progression from MCI due to AD through moderate dementia due to AD, and treatment effects that have been demonstrated across MCI and mild dementia due to AD (Honig et al. 2018; Wessels et al. 2020; Mintun et al. 2021). The iADRS has been validated (Wessels et al. 2015, 2018) and its statistical properties have been described. Meaningful within person change estimates for the iADRS have been defined (Wessels et al. 2022a) and associations with meaningful outcomes of disease, such as caregiver burden and quality of life, have been demonstrated (Wessels et al. 2022b).

Clinical Dementia Rating – Sum of Boxes (CDR-SB)

The CDR-SB is a semi structured interview performed with the patient and study partner (informant) that integrates domains of cognition and function into a single overall score (Berg et al. 1992; Morris 1993). By assigning a severity score for each of the 6 domains, and then summating each domain, a total score known as "Sum of Boxes" is obtained. Higher scores indicate greater disease severity. The CDR-SB (Hughes et al. 1982; Morris 1993) is a global assessment tool that can be used to effectively evaluate both cognition and function, with few floor or ceiling effects in a mild-to-moderate AD dementia population (Coley et al. 2011). The CDR global ratings, calculated using an algorithm, range from 0 (no dementia) to 3 (severe dementia) while CDR-SB scores, calculated by adding the box scores, range from 0 to 18 (with higher scores indicative of more impairment). Scoring is determined by a clinician through a semistructured and in-depth interview with both the affected individual and their study partner, rather than through direct testing. This scale demonstrates acceptable psychometric characteristics (Coley et al. 2011; Cedarbaum et al. 2013) and has been shown to be sensitive enough to detect disease progression, even in populations with less advanced clinical disease (Williams et al. 2013; Wessels et al. 2015).

Alzheimer's Disease Assessment Scale - Cognitive Subscale (13 Items) (ADAS-Cog 13)

The Alzheimer's Disease Assessment Scale – Cognitive subscale (ADAS-Cog13) is a rater-administered instrument that was designed to assess the severity of dysfunction in the cognitive and noncognitive behaviours characteristic of persons with AD (Rosen et al. 1984). The cognitive subscale of the ADAS, the ADAS-Cog13, consists of 13 items assessing areas of cognitive function that are the most typically impaired in AD: orientation, verbal memory, language, praxis, delayed free recall, digit cancellation, and maze-completion measures (Mohs et al. 1997). The ADAS-Cog13 scale ranges from 0 to 85, with higher scores indicating greater disease severity.

Alzheimer's Disease Cooperative Study - Activities of Daily Living Inventory – (ADCS-ADL)

The ADCS-ADL is a 23-item inventory developed as a rater-administered questionnaire that is to be answered by the patient's study partner (Galasko et al. 1997, 2004). The ADCS-ADL subset of items (items 6a and 7 to 23) for iADLs will be used as a secondary efficacy measure. The focus in the early symptomatic AD population is on the iADLs rather than the basic Activities of Daily Living (bADLs), which are thought to be affected in more severe stages of the disease. The range for the iADL score is 0 to 59, with lower scores indicating greater disease severity. For each of the specific items, the study partner is first asked if the patient attempted the ADL during the past 4 weeks. If the patient did attempt the ADL, the study partner is asked to rate the patient's performance level based on a set of performance descriptions. Scores for each item and the overall score for the tool are calculated. The range for the total ADCS-ADL score is 0 to 78, with higher scores indicating greater level of impairment.

Mini Mental State Examination (MMSE)

The Mini-Mental State Examination (MMSE) is a brief instrument used to assess cognitive function in patients (Folstein et al. 1975). The MMSE should be administered by the same rater from visit to visit to reduce potential variability. The instrument is divided into 2 sections. The first section measures orientation, memory, and attention. The maximum score for the first section is 21. The second section tests the ability of the patient to name objects, follow verbal and written commands, write a sentence, and copy figures. The maximum score for the second section is 9. The range for the total MMSE score is 0 to 30, with lower scores indicating great level of impairment.

Sample size

Study AACI was initially designed as a phase 2 study with CDR-SB progression as the primary endpoint and 500 participants. The protocol was later amended where the study was updated to a phase 3 trial with iADRS progression as primary endpoint (protocol amendment b). The sample size was increased to 1500 and later to 1800 participants.

In the final sample size calculation, a discontinuation rate of 30% was assumed. The final calculation assumed that 1000 low-medium tau participants would be included. Sample size calculation for phase 3 was initially based on an analysis using a Bayesian Disease Progression Model (BDP) and later, in protocol amendment e and final SAP, updated for an analysis using Natural Cubic Splines (NCS2). The observed effect size from the AACG trial was used to power the AACI trial. In the AACG trial, mean progression levels in the placebo and donanemab arms were estimated -10.06 and -6.86 points on iADRS (approximately 32% slowing) over 18 months, respectively, with a standard deviation of 11.06. In a simulation, the sample size of 1000 low-medium tau participants proved greater than 95% power to achieve statistical significance at a one-sided 2.5% level. To derive the total sample size for the overall population, it was assumed that approximately 2/3 of included participants were assumed to be low-medium tau participants.

Randomisation and blinding (masking)

Randomisation was 1:1 and stratified by 1) tau level (low-medium versus high) as decided by tau PET at screening and 2) study site. Assignment was determined by a computer-generated random sequence using an Interactive Web Response System.

This is a double-blind study and a minimal number of personnel will see the randomisation table and treatment assignments before the study is complete. Investigational product will be prepared by an unblinded pharmacist (or qualified personnel) and administered by a blinded nurse (or qualified personnel). The study investigator and site clinical study team will not have access to any florbetapir F18 results in order to maintain blinding to any potential changes in amyloid and tau deposition. Drug concentration information that may unblind the study will not be reported to investigative sites or blinded personnel until the study has been unblinded. The CDR rater should be blinded to AEs to avoid bias in the CDR assessment.

Emergency unblinding at a patient level for AEs was only to be used if the subject’s well-being requires knowledge of the subject’s treatment assignment. All unblinding events are recorded and reported by the IWRS.

The independent external data monitoring committee (DMC) is unblinded to randomisation.

Statistical methods

The Statistical Analysis Plan (SAP) for AACI was amended twice. The following table lists the substantial changes of each amendment.

*Table 6**:** Substantial changes per SAP version*

Sap version	Substantial changes
2	Study updated from phase 2 to phase 3. Primary endpoint changed from CDR-SB to iADRS. Primary analysis method changed from MRMM to Bayesian Disease Progression model (BDP). Sample size increased accordingly.
3	Primary analysis method changed to natural cubic spine with 2 degrees of freedom (NCS2)

Analysis sets

The following Table 7 list the analysis sets defined in the statistical analysis plan.

Table 7. Statistical analysis plan

Participant Analysis Set	Description
Entered	All participants who signed informed consent
Randomized	All entered participants who were randomly assigned to study treatment
Evaluable Efficacy	All randomly assigned participants with a baseline and at least one postbaseline efficacy scale
Safety	All randomly assigned participants who were exposed to study drug. Participants were summarized according to the treatment group to which they were randomly assigned.
Per-Protocol	All subjects in the Evaluable Efficacy population who also • signed the inform consent form • had an assessment of the primary endpoint at each scheduled visit completed • had no violations of inclusion/exclusion criteria • had no study dosing algorithm violation (such as if subjects randomly assigned to treatment A were given treatment B or subjects randomly assigned to treatment A never received the assigned study drug) • were not considered noncompliant with regard to study drug
Completers	All randomly assigned subjects who have disposition status of "complete."

Estimand

The primary estimand defined by the applicant contained the following attributes

Population: Participants with early symptomatic AD either with intermediate tau level at baseline (immediate tau population), or entire randomized participants including those with high tau value at baseline (overall population).

Endpoint: iADRS values at each visit to Week 76.

Treatment condition: Randomized treatment, donanemab or placebo, regardless of initiation or changes to standard of care medications and regardless of whether a participant stops taking the intervention (treatment policy strategy).

Intercurrent events: 'Initiation or change to standard of care medications' and 'discontinuation of donanemab', both will be handled by a treatment policy strategy

Population-level summary: the difference of adjusted mean change from baseline (CFB) values at 76 weeks between donanemab arm and the placebo arm.

With regard to the estimand definition it is noted that early symptomatic AD was not part of the inclusion criteria and that treatment condition attribute should include the switch to placebo as this was part of the treatment strategy specified in the protocol.

Statistical analyses

The SAP specifies that the evaluable efficacy set (EES) will be used for all efficacy analyses. The EES requires at least a baseline and post-baseline efficacy measurement to be available. Missing baseline measurements seem to be more frequent in the donanemab arm than in the placebo arm. In the low-medium tau pathology population, baseline measurement for the primary outcome at baseline is available for 560/594 (94%) subjects in the placebo arm and for 533/588 (91%) in the donanemab arm. These numbers are 824/876 (94%) for placebo and 775/860 (90%) for donanemab in the overall population.

Primary analysis uses a natural cubic spline model with 2 degrees of freedom (NCS2) to compare decline as measured by iADRS between intervention and placebo arm at 76 weeks. The iADRS score at baseline and each post-baseline visit are included as the dependent variable. Study visits are accounted for by including the time between baseline and post-baseline exam. Baseline estimates are restricted to be the same for the two groups. Analysis will be performed both in the low-medium tau pathology population and overall population. Analysis will be adjusted for baseline age, concomitant AchEI and/or memantine use at baseline (yes/no), and (pooled) investigator. Baseline tau category will also be included as a covariate to the model applied to overall population.

As a sensitivity analysis, MMRM analysis will be performed with change from baseline score on the iADRS at each scheduled postbaseline visit during the treatment period as dependent variable. The model will include fixed effects for: baseline score, baseline score-by-visit interaction, pooled investigator, treatment, visit, treatment-by-visit interaction, concomitant AChEI and/or memantine use at baseline (yes/no), and age at baseline. Visit will be considered a categorical variable and primary time point for treatment comparison will be the Week 76 visit.

As a second sensitivity analysis, slowing of iADRS progression with treatment of donanemab relative to placebo will be quantified through a disease progression ratio (DPR) derived from a Bayesian Disease Progression Model (DPM). Further, sensitivity analyses were defined that censored iADRS measurements post ARIA-E and imputed worst score at death as well as analysis in the completers and the per protocol set.

Secondary endpoint of CDR-SB will be assessed using MRMM and NCS2 (and similar models as for the primary analysis) separately in the intermediate tau population and overall population. ADAS-Cog13, ADCS-iADL, MMSE will only be assessed using NCS2 (and similar models as for the primary analysis) separately in the intermediate tau population and overall population. ADAS-Cog13 and ADCS-iADL were included in the hierarchical testing strategy, MMSE was not included.

Time progression models for the repeated measures (Time-PMRM) will be fitted for iADRS, CDR-SB, ADAS-Cog13, iADL and MMSE in both the intermediate tau and overall population. These models can be used to estimate the expected additional time required for the donanemab arm to reach the mean outcome level in the placebo arm at a specific post-baseline visit (disease progression time saved).

Change from baseline in plasma-based biomarkers including phosphorylated tau P-tau-217 and change from baseline in amyloid imaging centiloid (Amyloid CL) as measured by PET imaging and volumetric

MRI measurements will be analysed using a MRMM. Change from baseline in brain tau deposition SUVr values including tau PET frontal SUVr will be analyzed using ANCOVA with baseline tau SUVr, and age at baseline as covariates. Baseline tau category will also be included as a fixed effect to the models applied to overall population.

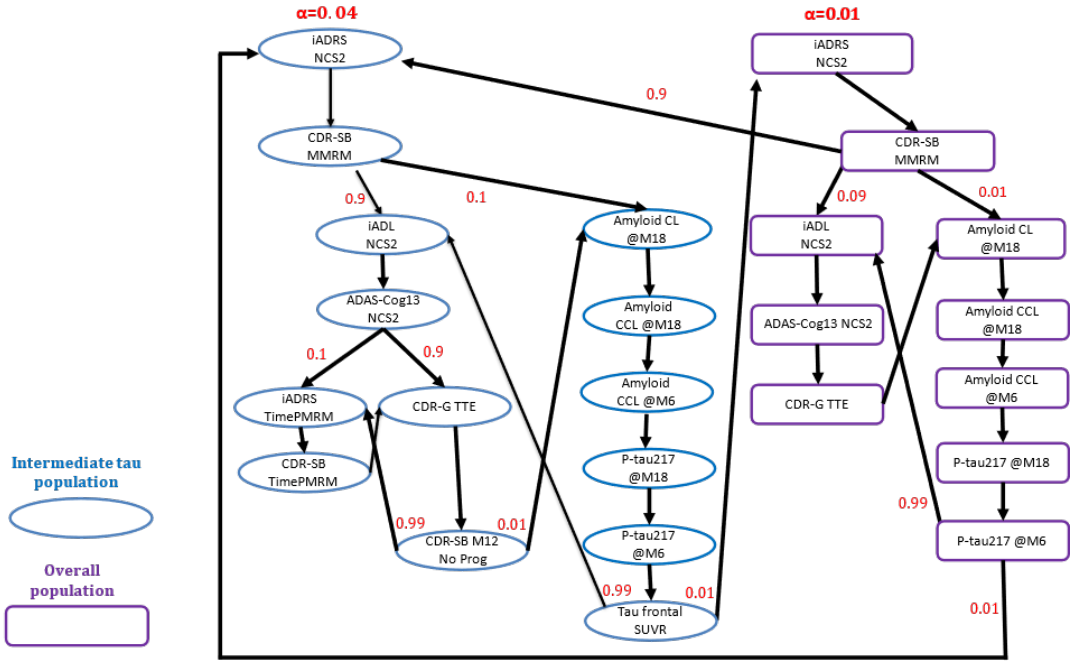
Tertiary endpoint of time to clinical worsening on CDR global scale (CDR-G TTE) will be analysed in the intermediate tau population using Cox regression where the event is defined as an increased CDR global score as compared to baseline at two consecutive visits during the double-blinded phase. Models will be adjusted for baseline age, baseline score, and concomitant AChEI and/or memantine use at baseline (yes/no) baseline tau category (for analysis in overall population) and stratified by pooled investigator sites.

Proportion of non-progressors on CBR-SB, defined as a CDR-SB change from baseline less than or equal to 0, will be analyzed in the intermediate tau population using a generalized linear mixed model with a fixed part similar to that of the MRMM used for primary and secondary endpoints.

Probability of amyloid complete removal (centiloid <24.1) among donanemab treated arm (Amyloid CCL) at will be tested with a binomial test, separately at week 24 and 76.

The type I error probability was controlled over the study at the two-sided 5% level through Bretz's graphical approach with 4% initially allocated to the intermediate tau population and 1% to the overall population. The hypothesis testing scheme, alpha recycle and weight, are described in detail in Figure 8.

Figure 8. Graphical testing procedure used for type I error control



No imputation strategies were defined for missing outcomes (e.g. due to missing visits), except for imputation of missing items on scales.

Results – study AACI

Participant flow

Number of patients

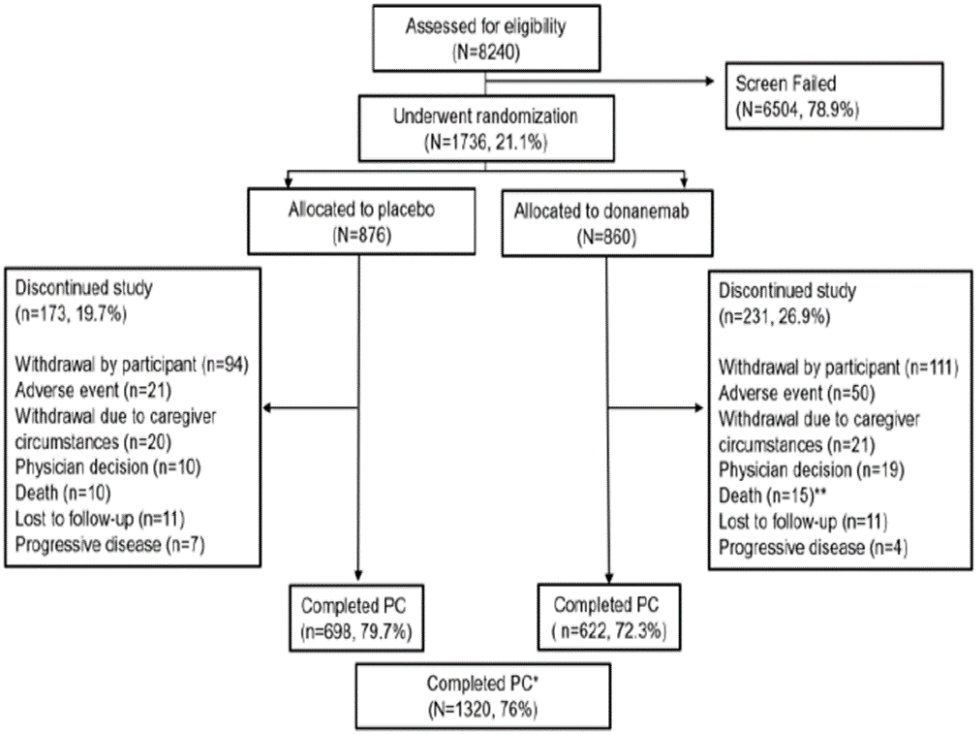
Planned: 1800 patients.

Randomised: 1736 patients (876 to placebo and 860 to donanemab).

Completed:1320 (76%) of patients completed the 76-week placebo-controlled phase (698 (79.7%) patients on placebo and 622 (72.3%) patients on donanemab).

Figure 9 shows the patients disposition for study AACI in the placebo-controlled phase.

Figure 9. Participant disposition for Study AACI-PC period.



Abbreviations: N = number of participants in the population; n = number of participants in the specified category; PC = placebo-controlled. * 12 participants did not complete final visit prior to database lock. ** 1 additional death occurred in the +57 day follow-up period. Source: Table AACI.8.1; Table AACI.8.2

Recruitment

Date first patient visit: 19 June 2020

Date last patient visit: 14 April 2023

Date Period data cut: 28 April 2023

This study was conducted at 277 centres that enrolled participants in eight countries including US, Canada, Australia, Netherlands, Poland, UK, Czech Republic, and Japan.

Conduct of the study

Table 8 summarises substantial changes in the conduct of Study AACI.

Table 8. Substantial changes in the conduct of Study AACI

Protocol Amendments	Substantial Changes
AACI (a)	In the original protocol, participants on the donanemab group were planned to receive 1400 mg every 4 weeks. Amendment (a) added a titration period of 700 mg for the first 3 doses due to higher-than-anticipated serious ARIA-E events relative to Phase 2.
AACI (b)	The amendment adapted Protocol AACI from a Phase 2 study to a Phase 3 study. The significant changes included • increase in the sample size • inclusion of P-tau as a pre-screening assessment, and its removal as an eligibility criterion from screening, and • changed in the primary analysis from "CDR-SB in overall population or intermediate tau population" to "iADRS in the intermediate tau population." The goal of the AACI study became to confirm Phase 2 results.
AACI (c)	The amendment increased the sample size by approximately 300 participants and defined approximately 300 early enrolled participants as Cohort 1. Cohort 1 was planned to be unblinded to the sponsor to inform analyses of safety and efficacy of donanemab and planning of future studies in AD. Sites, participants, and study partners remained blinded. The plan to unblind Cohort 1 was eventually removed as part of Amendment e (mentioned below).
AACI (d)	The significant changes included the following: • The amendment added a long-term extension phase to this study to further evaluate the efficacy and safety of donanemab over time. • The Week 4 MRI was initially conducted only in Japan until this protocol amendment (d), which added the Week 4 MRI globally. The Week 4 MRI was used to check for evidence of ARIA-E or -H and other clinically relevant safety findings. Unscheduled MRIs could be performed at the discretion of the investigator.
AACI (e)	This amendment removed references to Cohort 1 and Cohort 2 analyses. This amendment also updated the analysis method from Bayesian Disease Progression Model to NCS for the primary objective.

Abbreviations: AD = Alzheimer's disease; ARIA-E = amyloid-related imaging abnormalities–oedema/effusions (also known as vasogenic oedema); ARIA-H = amyloid-related imaging abnormalities–haemorrhage/haemosiderin deposition (including brain microhaemorrhage and superficial siderosis); CDR-SB = Clinical Dementia Rating Scale – Sum of Boxes; iADRS = integrated Alzheimer's Disease Rating Scale; MRI = magnetic resonance imaging; NCS = natural cubic spline.

Protocol deviations

Overall, 71.6% of all patients had at least one important protocol deviation, and the incidence of important deviations was similar across all treatment groups. The most common major deviations (≥ 20% total participants) were in the categories of study procedures compliance (49.4%), investigational medicinal product (26.5%), informed consent (21.3%) and safety reporting (9.6%).

GCP

Three sites were closed during this trial due to GCP noncompliance. All available safety and efficacy data followed the predefined criteria in the SAP for the trial and were either included or not included based on these criteria. In total this concerns 63 patients.

Baseline data

Based on their tau deposition patients were divided into an intermediate tau population or in the overall population. Intermediate tau population included patients with low–medium tau pathology. The overall population included all randomised patients (also the patients with high tau pathology).

Low-medium tau was defined as: SUVr ≤1.46 and a topographic deposition pattern consistent with advanced AD (AD++) or, 1.10 ≤ SUVr ≤ 1.46 and a topographic deposition pattern consistent with moderate AD (AD+).

High tau: SUVr >1.46 and a topographic deposition pattern consistent with either moderate (AD+) or advanced AD (AD++).

Table 9 describes the baseline data for the two populations: the intermediate tau population and the overall population. Overall, the baseline demography, clinical, and biomarker measures were well balanced between the donanemab and placebo groups.

Table 9. Summary of demographics and characteristics of participants at baseline study I5T-MC-AACI (AACI-PC Period) ITT population(Table made by assessor)

	Intermediate Tau Population			Overall Population		
Demographics [a]	**Placebo (N = 594)**	**Donanemab (N = 588)**	**Total (N = 1182)**	**Placebo (N = 876)**	**Donanemab (N = 860)**	**Total (N = 1736)**
Female sex, n(%)	321 (54.0)	325 (55.3)	646 (54.7)	503 (57.4)	493 (57.3)	996 (57.4)
Mean age, years (SD)	74.3 (5.8)	74.3 (5.7)	74.3 (5.7)	73.0 (6.2)	73.0 (6.2)	73.0 (6.2)
Education, ≥13 years, n(%)	421 (71.0)	407 (69.2)	828 (70.1)	637 (72.8)	606 (70.5)	1243 (71.7)
APOE4 carrier, n(%)	427 (72.3)	421 (71.7)	848 (72.0)	621 (71.2)	598 (69.8)	1219 (70.5)
APOE genotypes, n(%)						
E2/E2	1 (0.2)	0 (0.0)	1 (0.1)	1 (0.1)	0 (0.0)	1 (0.1)
E2/E3	14 (2.4)	10 (1.7)	24 (2.0)	20 (2.3)	18 (2.1)	38 (2.2)
E2/E4	19 (3.2)	17 (2.9)	36 (3.1)	25 (2.9)	22 (2.6)	47 (2.7)
E3/E3	149 (25.2)	156 (26.6)	305 (25.9)	230 (26.4)	241 (28.1)	471 (27.2)
E3/E4	308 (52.1)	314 (53.5)	622 (52.8)	450 (51.6)	433 (50.5)	883 (51.1)
E4/E4	100 (16.9)	90 (15.3)	190 (16.1)	146 (16.7)	143 (16.7)	289 (16.7)
Missing	3	1	4	4	3	7
AchEI use, n(%)	307 (51.7)	305 (51.9)	612 (51.8)	488 (55.7)	478 (55.6)	966 (55.6)
Memantine use, n(%)	118 (19.9)	112 (19.0)	230 (19.5)	180 (20.5)	172 (20.0)	352 (20.3)
AchEI and/or memantine use, n(%)	341 (57.4)	332 (56.5)	673 (56.9)	538 (61.4)	521 (60.6)	1059 (61.0)
Scale						
iADRS, mean (SD)	105.5 (13.7)	105.7 (13.8)	105.6 (13.8)	103.6 (14.0)	104.1 (14.3)	103.8 (14.2)
CDR-SB, mean (SD)	3.7 (2.0)	3.7 (2.1)	3.7 (2.1)	3.9 (2.1)	4.0 (2.1)	3.9 (2.1)
ADASCog13, mean (SD)	27.8 (8.4)	27.5 (8.5)	27.7 (8.4)	29.3 (8.9)	28.7 (8.8)	29.0 (8.9)
ADCS-ADL, mean (SD)	66.9 (8.5)	66.7 (8.5)	66.8 (8.5)	66.4 (8.3)	66.3 (8.6)	66.4 (8.5)
ADCS-iADL, mean (SD)	48.4 (7.9)	48.1 (7.9)	48.2 (7.9)	47.8 (7.8)	47.8 (7.9)	47.8 (7.9)
MMSE [b], mean (SD)	22.8 (3.8)	23.1 (3.6)	22.9 (3.7)	22.2 (3.9)	22.4 (3.8)	22.3 (3.9)
CDR – Global Score n(%)						
0	3 (0.5)	2 (0.3)	5 (0.4)	4 (0.5)	2 (0.2)	6 (0.4)
0.5	387 (65.5)	382 (65.9)	769 (65.7)	532 (61.2)	514 (60.8)	1046 (61.0)
1	185 (31.3)	177 (30.5)	362 (30.9)	308 (35.4)	304 (36.0)	612 (35.7)
2	16 (2.7)	19 (3.3)	35 (3.0)	25 (2.9)	25 (3.0)	50 (2.9)
Missing	3	8	11	7	15	22
Amyloid PET Centiloids, mean (SD)	100.9 (35.1)	102.4 (34.7)	101.6 (34.9)	101.6 (34.5)	103.5 (34.5)	102.5 (34.5)
AD signature weighted neocortical flortaucipir SUVr, mean (SD)	1.2 (0.1)	1.2 (0.1)	1.2 (0.1)	1.4 (0.3)	1.3 (0.3)	1.3 (0.3)

Abbreviations: ADAS-Cog13 = Alzheimer's Disease Assessment Scale –13-item Cognitive subscale; ADCS-ADL = Alzheimer's Disease Cooperative Study – Activities of Daily Living scale; ADCS-iADL=Alzheimer's Disease Cooperative Study – instrumental Activities of Daily Living subscale; APOE4 = apolipoprotein E allele 4; AchEI = acetylcholinesterase inhibitor; CDR-SB = Clinical Dementia Rating Scale – Sum of Boxes; iADRS = integrated Alzheimer's Disease Rating Scale; MMSE = Mini-Mental State Examination; MUBADA = multiblock barycentric discriminant analysis (method of analysing PET images); N = number of participants in the population; n = number of participants in the specified category; PC = placebo-controlled; PET = positron emission tomography; SD = standard deviation; SUVr = standardized uptake value ratio. a For all categories, the number of subjects with nonmissing data was used as the denominator. b Last nonmissing MMSE prior to or on start of study treatment. Source: Table AACI.8.3; Table AACI.8.4 Table made by assessor based on Table AACI.4.4 and AACI.4.5. CSR study AACI

Numbers analysed

All efficacy analyses seem to have been performed in the Evaluable Efficacy Set (EES) containing only subjects randomized with at least a baseline and one post-baseline measurement. The number of participants in each analysis may therefore differ between endpoints.

For this reason, in the summary of results in this report the number of participants with a baseline measurement for the specific endpoint is reported in the tables which may be higher than the number in the EES population used for the specific analysis. Analyses used the ITT principle with participants being analyzed in the treatment group to which they were analyzed.

Outcomes and estimation

Primary endpoint

IADRS

The primary endpoint was Change from Baseline in iADRS at week 76. The mean difference in change from baseline in iADRS at week 76 between donanemab and placebo in the APOE-E4 non-carriers population was 2.02 (p=0.14). The mean difference in change from baseline in iADRS at week 76 between donanemab and placebo in the overall population was 1.58, (p=.026), see Table 10.

Table 10. MMRM: Change from baseline in iADRS at Week 76 (ITT)

	Non-carriers population		**Overall population**	
iADRS	**Placebo** N = 251	**Donanemab** N = 259	**Placebo** N = 876	**Donanemab** N = 860
Baseline score mean (SD)	102.00 (14.31)	103.61 (14.60)	103.50 (14.05)	104.06 (14.28)
Score at week 76 mean (SD)	85.92 (23.76)	90.26 (24.69)	90.34 (22.73)	92.98 (23.23)
Change week 76 LS mean change (se)	-15.84 (1.01)	-13.58 (0.96)	-13.06 (0.52)	-11.16 (0.51)
LS mean Change Difference versus placebo at week 76 (%)		2.26 (14.3)		1.90 (14.5)
95% Confidence interval		-0.435,4.952		0.502, 3.289
p-value		0.10		0.0077

Abbreviations: iADRS = integrated Alzheimer's Disease Rating Scale; LS = least squares; MMRM = Mixed Model for Repeated Measures; PC = placebo-controlled; SE = standard error. MRMM analyses performed in ITT (intent-to-treat) population that included all randomized participants; post hoc sensitivity analyses using methods for handling missing data (jump-to reference-imputation).

Secondary endpoints

CDR-SB

The Change from Baseline in CDR-SB at week 76 as analyzed with MRMM was a secondary endpoint included in the graphical testing strategy. The mean difference in change from baseline at week 76 between donanemab and placebo in the APOE-E4 non-carriers population was -0.51 (p=0.05). The

mean difference in change from baseline at week 76 between donanemab and placebo in the overall population was -0.47 (p<0.001), see Table 11.

Table 11. MMRM: Change from baseline in CDR-SB at Week 76 (ITT)

	Non-carriers population		Overall population	
CDR-SB	**Placebo** N = 251	**Donanemab** N = 259	**Placebo** N = 876	**Donanemab** N = 860
Baseline score mean (SD)	4.18 (2.10)	3.96 (2.17)	3.93 (2.07)	3.96 (2.09)
Score at week 76 mean (SD)	6.91 (3.85)	6.13 (3.52)	6.32 (3.58)	5.82 (3.44)
Change week 76 LS mean change (se)	2.73 (0.19)	2.17 (0.18)	2.39 (0.09)	1.86 (0.09)
LS mean Change Difference versus placebo at week 76 (%)		-0.56 (20.7)		-0.53 (22.1)
95% Confidence interval		-1.064, -0.065		-0.769, -0.287
p-value		0.027		<0.0001

Abbreviations: CDR-SB = Clinical Dementia Rating Scale – Sum of Boxes; LS = least squares; MMRM = Mixed Model for Repeated Measures; PC = placebo-controlled; SE = standard error. MRMM analyses performed in ITT (intent-to-treat) population that included all randomized participants; post hoc sensitivity analyses using methods for handling missing data (jump-to reference-imputation).

ADAS-Cog13

The Change from Baseline in ADAS-Cog13 at week 76 was a secondary endpoint included in the graphical testing strategy. The mean difference in change from baseline at week 76 between donanemab and placebo in the APOE-E4 non-carriers population was -1.16 (p=0.12). The mean difference in change from baseline at week 76 between donanemab and placebo in the overall population was -0.68 (p=0.088), see Table 12.

Table 12. MMRM: Change from baseline in ADAS-Cog13 at Week 76 (ITT)

	Non-carriers population		Overall population	
ADAS-Cog13	**Placebo** N = 251	**Donanemab** N = 259	**Placebo** N = 876	**Donanemab** N = 860
Baseline score mean (SD)	29.67 (9.01)	28.72 (8.85)	29.30 (8.91)	28.73 (8.83)
Score at week 76 mean (SD)	37.98 (13.07)	35.83 (13.95)	36.16 (12.82)	34.69 (13.2)
Change week 76 LS mean change (se)	8.34 (0.53)	7.09 (0.51)	6.81 (0.29)	6.02 (0.29)
LS mean Change Difference versus placebo at week 76 (%)		-1.25 (15.0)		-0.79 (11.7)
95% Confidence interval		-2.722, 0.222		-1.567, -0.022
p-value		0.096		0.0439

Abbreviations: ADAS-Cog13 = Alzheimer's Disease Assessment Scale – 13-item Cognitive subscale; LS = least squares; MMRM = Mixed Model for Repeated Measures; PC = placebo-controlled; SE = standard error. MRMM analyses performed in ITT (intent-to-treat) population that included all randomized participants; post hoc sensitivity analyses using methods for handling missing data (jump-to reference-imputation).

ADCS-iADL

The Change from Baseline in ADCS-iADL at week 76 was a secondary endpoint included in the graphical testing strategy. The mean difference in change from baseline at week 76 between donanemab and placebo in the APOE-E4 non-carriers population was 1.31 (p=0.15). The mean difference in change from baseline at week 76 between donanemab and placebo in the overall population was 1.21 (p=0.006), see Table *13*.

Table 13. MMRM: Change from baseline in ADCS-iADL at Week 76 (ITT) (made by the assessor)

	Non-carriers population		**Overall population**	
ADCS-iADL	**Placebo** N = 251	**Donanemab** N = 259	**Placebo** N = 876	**Donanemab** N = 860
Baseline score mean (SD)	46.72 (8.23)	47.35 (8.17)	47.82 (7.81)	47.75 (7.91)
Score at week 76 mean (SD)	38.92 (12.93)	41.18 (12.62)	41.65 (11.82)	42.85 (12.04)
Change week 76 LS mean change (se)	-7.64 (0.64)	-6.32 (0.64)	-6.13 (0.32)	-4.92 (0.32)
LS mean Change Difference versus placebo at week 76 (%)		1.31 (17.2)		1.21 (19.8)
95% Confidence interval		-0.474, 3.097		0.352, 2.076
p-value		0.1499		0.0058

Abbreviations: ADCS-iADL = Alzheimer's Disease Cooperative Study – instrumental Activities of Daily Living subscale; LS = least squares; MMRM = Mixed Model for Repeated Measures; PC = placebo-controlled; SE = standard error. MRMM analyses performed in ITT (intent-to-treat) population that included all randomized participants; post hoc sensitivity analyses using methods for handling missing data (jump-to reference-imputation). Table made by assessor based on responses to the D233 questions.

MMSE

The mean difference in change from baseline at week 76 between donanemab and placebo in the APOE-E4 non-carriers population was 0.24 (p=0.52). The mean difference in change from baseline at week 76 between donanemab and placebo in the overall population was 0.24 (p=0.23), see Table 14.

Table 14. MMRM: Change from baseline in MMSE at Week 76 (ITT) (made by the assessor)

	Non-carriers population		Overall population	
MMSE	**Placebo** N = 251	**Donanemab** N = 259	**Placebo** N = 876	**Donanemab** N = 860
Baseline score mean (SD)	21.89 (3.79)	22.13 (4.01)	22.14 (3.91)	22.42 (3.83)
Score at week 76 mean (SD)	18.38 (5.8)	18.89 (6.01)	19.15 (5.8)	19.69 (5.78)
Change week 76 LS mean change (se)	-3.50 (0.27)	-3.26 (0.26)	-2.98 (0.14)	-2.74 (0.14)
LS mean Change Difference versus placebo at week 76 (%)		0.24 (7.0)		0.24 (8.0)
95% Confidence interval		-0.508, 0.998		-0.154, 0.632
p-value		0.5235		0.2328

MMSE= Mini-Mental State Examination; LS = least squares; MMRM = Mixed Model for Repeated Measures; PC = placebo-controlled; SE = standard error. MRMM analyses performed in ITT (intent-to-treat) population that included all randomized participants; post hoc sensitivity analyses using methods for handling missing data (jump-to reference-imputation). Table made by assessor based responses to the D233 questions.

High tau only subgroup

In the high tau only subgroup of the APOE-E4 non-carriers, no differences were observed between placebo and donanemab, see Table 15.

Table 15. MMRM: Change from baseline in iADRS and CDR-SB at week 76 (ITT) for the restricted population of APOE-E4 non-carriers only (made by the assessor)

Noncarriers with High tau population	**iADRS**		**CDR-SB**	
	Placebo N = 87	**Donanemab** N = 93	**Placebo** N = 87	**Donanemab** N = 93
Baseline score mean (SD)	97.78 (14.50)	101.47 (14.92)	4.71 (1.86)	4.45 (1.83)
Score at week 76 mean (SD)	75.70 (23.22)	80.05 (28.90)	8.17 (3.79)	7.50 (3.59)
Change week 76 LS mean change (se)	-21.58 (1.83)	-21.89 (1.82)	3.40 (0.335)	3.10 (0.32)
LS mean Change Difference versus placebo at week 76 (%)		-0.32 (1.5 increase)		-0.30 (9.0)
95% Confidence interval		-5.417, 4.786		-1.224, 0.614
p-value		0.9034		0.5153

Abbreviations: iADRS = integrated Alzheimer's Disease Rating Scale; CDR-SB = Clinical Dementia Rating Scale – Sum of Boxes; LS = least squares; MMRM = Mixed Model for Repeated Measures; PC = placebo-controlled; SE = standard error. MRMM analyses performed in ITT (intent-to-treat) population that included all randomized participants; post hoc sensitivity analyses using methods for handling missing data (jump-to reference-imputation). Table made by assessor based on responses to the D233 questions.

Tertiary endpoints

Slowing of disease progression time

Time saved progression analyses (saved (absolute in months and relative) based on the nonproportional PMRM analysis, under the assumptions as described above, for all primary and secondary endpoints in the intermediate and overall population were provided for the primary and some of the secondary outcomes, see Table 16.

Table 16. Time-saved progression model for repeated measures at Week 76, intermediate tau population Study I5T-MC-AACI (AACI-PC period)

	Noncarriers population			
	iADRS[a]	CDR-SB	ADAS-Cog13	ADCS-iADL
Time saved (in months) (95% CI)	1.6 (-0.23, 3.36)	2.71 (-0.65, 6.06)	1.12 (-0.59, 2.85)	1.57 (-0.22, 3.36)
	Overall population			
	iADRS[a]	CDR-SB	ADAS-Cog13	ADCS-iADL
Time saved (in months) (95% CI)	1.2 (0.1, 2.2)	3.1 (1.3, 4.8)	0.8 (-0.1, 1.8)	2.1 (0.4, 3.8)

Abbreviations: ADAS-Cog13 = Alzheimer's Disease Assessment Scale –13-item Cognitive subscale; ADCS-ADL = Alzheimer's Disease Cooperative Study – Activities of Daily Living scale; ADCS-iADL=Alzheimer's Disease Cooperative Study – instrumental Activities of Daily Living subscale; CDR-SB = Clinical Dementia Rating Scale – Sum of Boxes; iADRS = integrated Alzheimer's Disease Rating Scale.

Probability of non-progression

To further evaluate the treatment benefit of donanemab, participants' status was classified as "nonprogressing" if their CDR-SB change from baseline was less than or equal to 0 at each of the scheduled visits. A GLMM was applied to assess the difference in probability of "nonprogressing" at each timepoint by treatment group. At Week 76, 19% of donanemab-treated participants in the APOE-E4 non-carriers population compared with 14% of placebo-treated participants remained stable (showed no decline in CDR-SB from baseline) (p=0.12). A total of 36% of donanemab-treated participants in the overall population compared with 23% of placebo-treated participants remained stable (nominal p<.00001).

Long-term extension data

No efficacy data of the long-term extension phase of the pivotal study has been provided.

Correlations between biomarkers and iADRS/CDR-SB

To assess the relationship of biomarker with cognition and function with treatment, Spearman's rank correlation coefficient was obtained on change from baseline at each follow-up visit between biomarker change and change from baseline to Week 76 for iADRS and CDR-SB. Correlation analyses were conducted by including participants from both treatment groups for amyloid CL reduction, P-tau217, GFAP and tau SUVR. All the correlation coefficients for these analyses in this section ranged between -0.19 and 0.16.

Ancillary analyses

Subgroup analyses

Subgroup analyses were provided for the overall population, including all APOE-E4 genotypes.

Figure 10. NCS2: Subgroup analysis of iADRS, combined population (AACI-PC period)

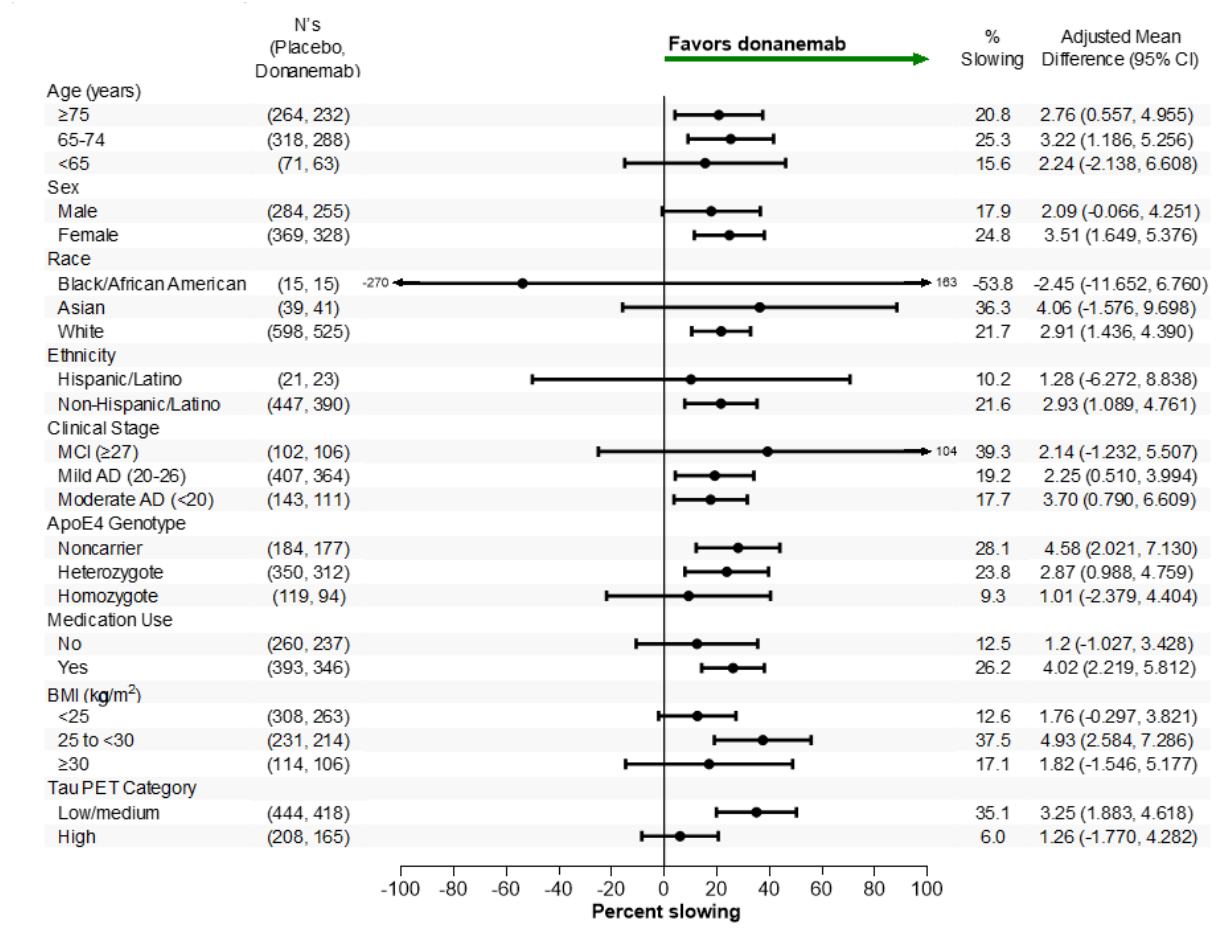
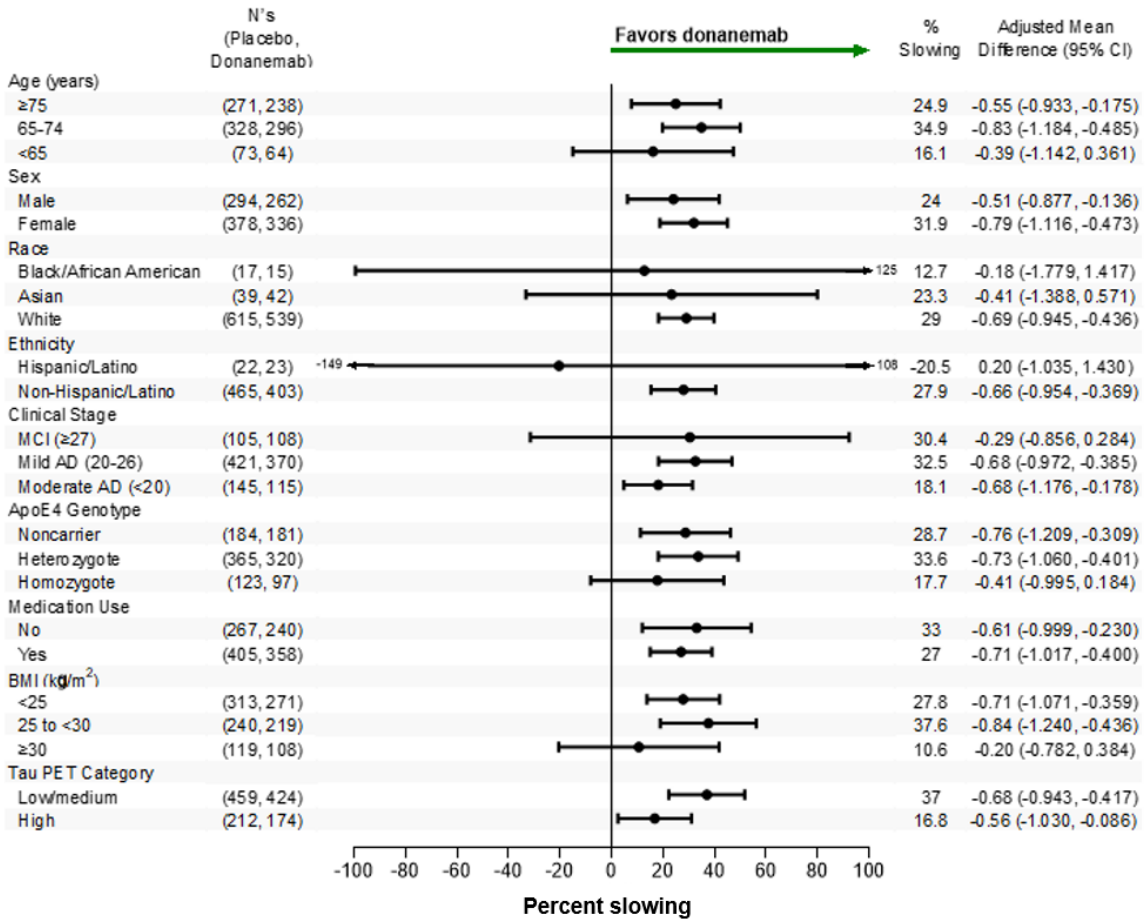


Figure 11. NCS2: Subgroup analysis of CDR-SB, combined population (AACI-PC period).



Abbreviations for both figures on subgroup analyses: AACI-PC = placebo-controlled period of Study AACI; AD = Alzheimer's disease; ApoE4 = allele subtype 4 of the gene coding for apolipoprotein class E; BMI = body mass index; CI = confidence interval; iADRS = integrated Alzheimer's Disease Rating Scale; MCI = mild cognitive impairment; N= number of participants; NCS2 = natural cubic spline with 2 degrees of freedom.

Sensitivity analyses

The primary and secondary outcome measures for the originally sought indication (including all APOE-E4 genotypes) were analysed across different statistical models like the MMRM, DPM and NCS3. In addition, sensitivity analyses were performed for iADRS that censored observations after first occurrence of ARIA-E or assigned the worst possible score of 0 post-death. All models included a similar set of covariates and made a similar missingness at random assumption regarding missing outcomes.

Long-term extension (LTE)

At a late stage of the evaluation procedure, the applicant submitted preliminary data from the LTE phase of study AACI. These data mainly concern the broad population including all APOE-E4 genotypes, and not the sought restricted population of APOE-E4 non-carriers only. In addition, and with a degree of uncertainty given to the insufficient details provided, analyses seemed to be performed in the EES, and not in the ITT. Moreover, conducted analyses (including assumptions for missing data) are not clearly described.

- **Summary of main efficacy results**

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 17. Summary of efficacy for trial AACI

<table>
<tr><td colspan="6">Title: A Phase 3, double-blind, placebo-controlled study to evaluate the safety and efficacy of donanemab in patients with early symptomatic AD (mild cognitive impairment and mild dementia due to AD) with the presence of brain amyloid and tau pathology over 76 weeks of the double-blind period.</td></tr>
<tr><td>Study identifier</td><td colspan="5">I5T-MC-AACI; 2020-000077-25</td></tr>
<tr><td>Design</td><td colspan="5">A Phase 3, multicentre, randomised, parallel-group, double-blind, placebo-controlled study</td></tr>
<tr><td></td><td colspan="2">Duration of main phase:
Duration of Run-in phase:
Duration of Extension phase:</td><td colspan="3">76 weeks
not applicable
78 weeks extension + 44 weeks FU</td></tr>
<tr><td>Hypothesis</td><td colspan="5">Superiority</td></tr>
<tr><td rowspan="2">Treatments groups</td><td colspan="2">Placebo IV Q4W</td><td colspan="3">Number randomised
Overall population = 876
Restricted population = 251</td></tr>
<tr><td colspan="2">Donanemab 700 mg IV Q4W for the first 3 doses, then 1400 mg IV Q4W</td><td colspan="3">Number randomised
Overall population = 860
Restricted population = 259</td></tr>
<tr><td rowspan="2">Endpoints and definitions</td><td>Primary endpoint</td><td>iADRS</td><td colspan="3">change from baseline through Week 76 in at least 1 of the study populations</td></tr>
<tr><td>Secondary endpoints</td><td>CDR-SB
ADAS-COG13
ADCS-iADL
MMSE</td><td colspan="3">Change from baseline through Week 76 in at least 1 of the study populations</td></tr>
<tr><td>Database lock</td><td colspan="5">28 April 2023</td></tr>
<tr><td colspan="6"><u>Results and Analysis</u></td></tr>
<tr><td>Analysis description</td><td colspan="5">Primary Analysis</td></tr>
<tr><td>Analysis population and time point description</td><td colspan="5">MRMM analyses in the ITT population for primary and all secondary outcomes, with missing data imputed using a jump to reference method.</td></tr>
<tr><td rowspan="2">Descriptive statistics and estimate variability</td><td>Treatment group</td><td colspan="2">Restricted population
APOE-E4 non-carriers only</td><td colspan="2">Overall population
All APOE-E4 genotypes</td></tr>
<tr><td></td><td>Placebo</td><td>Donanemab</td><td>Placebo</td><td>Donanemab</td></tr>
</table>

	Number of subjects	251	259	876	860
	iADRS LS mean change (se)	-15.84 (1.01)	-13.58 (0.96)	-13.06 (0.52)	-11.16 (0.51)
	CDR-SB LS mean change (se)	2.73 (0.188)	2.17 (0.180)	2.39 (0.091)	1.86 (0.091)
	ADAS-COG13 LS mean change (se)	8.34 (0.533)	7.09 (0.509)	6.81 (0.293)	6.02 (0.287)
	ADCS-iADL LS mean change (se)	-7.64 (0.639)	-6.32 (0.637)	-6.13 (0.322)	-4.92 (0.319)
	MMSE LS mean change (se)	-3.50 (0.269)	-3.26 (0.264)	-2.98 (0.140)	-2.74 (0.143)
Effect estimate per comparison	Primary endpoint Change from baseline in iADRS at Week 76	Comparison groups		**Non-carriers population** Placebo vs Donanemab	
		LS mean change diff. (%)		2.26 (14.3)	
		95% confidence interval		-0.435,4.952	
		P-value		0.1000	
				Overall population Placebo vs Donanemab	
		LS mean change diff. (%)		1.90 (14.5)	
		95% confidence interval		0.502, 3.289	
		P-value		0.0077	
	Secondary endpoint CDR-SB	Comparison groups		**Non-carriers population** Placebo vs Donanemab	
		LS mean change diff. (%)		-0.56 (20.7)	
		95% confidence interval		-1.064, -0.065	
		P-value		0.0269	
				Overall population Placebo vs Donanemab	
		LS mean change diff. (%)		-0.53 (22.1)	
		95% confidence interval		-0.769, -0.287	
		P-value		<0.0001	
	Secondary endpoint ADAS-COG13	Comparison groups		**Non-carriers population** Placebo vs Donanemab	
		LS mean change diff. (%)		-1.25 (15.0)	
		95% confidence interval		-2.722, 0.222	
		P-value		0.096	
				Overall population Placebo vs Donanemab	
		LS mean change diff. (%)		-0.79 (11.7)	
		95% confidence interval		5.452, 6.578	
		P-value		0.0439	
	Secondary endpoint ADCS-iADL	Comparison groups		**Non-carriers population** Placebo vs Donanemab	
		LS mean change diff. (%)		1.31 (17.2)	
		95% confidence interval		-0.474, 3.097	
		P-value		0.1499	
				Overall population Placebo vs Donanemab	
		LS mean change diff. (%)		1.21 (19.8)	
		95% confidence interval		0.352, 2.076	
		P-value		0.0058	

	Secondary endpoint MMSE	Comparison groups	**Non-carriers population** Placebo vs Donanemab
		LS mean change diff. (%)	0.24 (7.0)
		95% confidence interval	-0.508, 0.998
		P-value	0.5235
			Overall population Placebo vs Donanemab
		LS mean change diff. (%)	0.24 (8.0)
		95% confidence interval	-0.154, 0.632
		P-value	0.2328
Notes	Changes at week 76 are adjusted for several baseline factors and for some endpoints estimated using natural cubic spline model. Therefore, the LS mean change (se) may not exactly match with the mean score at week 76 - mean baseline score. The applicant prefers analyses in the Evaluable Efficacy Set (EES) under a missingness at random assumption. The exclusion criteria for the EES set also include the availability of a post-baseline measurement which may depend on the treatment received (e.g. through early AEs) which may introduce selection bias. In addition, proportion of study discontinuations was large in both arms (20-25%) which could severely impact estimates in case missingness is not at random (which is expected to be the case to some extent). For this reason, conservative estimates in the ITT analysis using a jump-to-reference imputation method are presented here, rather than the primary analyses as presented by the applicant.		

2.6.5.3. Clinical studies in special populations

No dose adjustments are foreseen in patients with renal or hepatic impairment given that this is an immunoglobulin and the clearance is not expected to be affected by renal or hepatic impairment.

As part of the D120 answers, the applicant provided the following table:

Table 18. Older subjects age groups in controlled and non-controlled trials.

	Age 65-74 (Older Subjects Number/Total Number)	**Age 75-84 (Older Subjects Number/Total Number)**	**Age 85+ (Older Subjects Number/Total Number)**
Controlled trials	917/1983	846/1983	36/1983
Non-controlled trials	438/1118	584/1118	25/1118

Note: Controlled trials - Study AACG and Study AACI (main placebo-controlled period), non-controlled trials - Study AACI (Safety Addendum) and Study AACN.

2.6.5.4. Supportive study AACG

Study AACG was a randomised, double-blind, placebo-controlled study in 272 patients with MCI due to AD and mild AD with an intermediate tau load. Patients received 3 infusions of 700mg donanemab Q4W and then 1400mg Q4W or placebo Q4W up to Week 72. The in- and exclusion criteria were in principle the same as for pivotal Study AACI. Though, only patients with low or medium tau load were included.

Primary objective was to test the hypothesis that donanemab administered for up to 72 weeks will decrease the cognitive and/or functional decline in patients with early symptomatic AD. Primary endpoint of this study was the change from baseline to week 76 on the integrated Alzheimer's Disease

Rating Scale (iADrs). The effect of donanemab on Aβ plaque was one of the secondary objectives and PET scans were conducted at week 24, 52 and 76.

The statistical methods were a mixed model repeated measure (MMRM) with covariate adjustments. The primary comparison was donanemab versus placebo.

Results

Table 19 shows the results for the primary (iADRS) and secondary endpoints for study AACG.

Table 19. Mixed model for repeated measures: primary and secondary endpoints double-blind treatment period full analysis set I5T-MC-AACG (table made by assessor)

	iADRS		CDR-SB		ADAS-Cog13		ADCS-iADL		MMSE	
	Placebo N = 120	Donanemab N = 125	Placebo N = 120	Donanemab N = 125	Placebo N = 120	Donanemab N = 125	Placebo N = 120	Donanemab N = 125	Placebo N = 115	Donanemab N = 121
Baseline score mean (SD)	106.06 (13.05)	106.30 (12.73)	3.37 (1.70)	3.55 (2.04)	27.53 (7.55)	27.68 (7.70)	48.58 (7.42)	48.98 (7.24)	23.77 (2.88)	23.77 (2.88)
Score week 76 mean (SD)	96.69 (18.59)	99.29 (17.49)	4.89 (2.56)	4.84 (2.56)	32.43 (9.61)	30.54 (10.02)	44.22 (10.85)	44.83 (10.343)	20.59 (4.790)	21.14 (4.71)
Change week 76 LS mean change (se)	-10.06 (1.14)	-6.86 (1.14)	1.58 (0.18)	1.22 (0.18)	4.77 (0.66)	2.91 (0.659)	-5.20 (0.74)	-3.98 (0.738)	-2.98 (0.390)	-2.35 (0.39)
LS mean Change Difference versus placebo week 76 (%)		3.20 (32%)		-0.36 (23%)		-1.86 (39%)		1.21 (23%)		0.64 (21%)
95% Confidence interval		0.12, 6.27		-0.83, 0.12		-3.63, -0.09		-0.77, 3.20		-0.40, 1.67
p-value		.04		.14		.04		.23		.23

Abbreviations: ADAS-Cog13 = Alzheimer's Disease Assessment Scale –13-item Cognitive subscale; ADCS-ADL = Alzheimer's Disease Cooperative Study – Activities of Daily Living scale; ADCS-iADL=Alzheimer's Disease Cooperative Study – instrumental Activities of Daily Living subscale; CDR-SB = Clinical Dementia Rating Scale – Sum of Boxes; iADRS = integrated Alzheimer's Disease Rating Scale; MMSE = Mini-Mental State Examination. Note that change at week 76 are adjusted for several baseline factors. Therefore, the LS mean change (se) may not exactly match with the mean score at week 76 - mean baseline score. Based on Tables AACG.5.1.-AACG.5.5. CSR study AACG

2.6.6. Discussion on clinical efficacy

Design and conduct of clinical studies

One single pivotal phase 3 study AACI and a supportive phase 2 study AACG are submitted in support of the MAA. During the course of the MAA, the originally broad indication of patients with MCI due to AD or Mild AD, was restricted to exclude APOE-E4 homozygous patients, and then further restricted to APOE-E4 non-carriers only: "Donanemab is indicated for the treatment of adult patients with a clinical diagnosis of mild cognitive impairment and mild AD dementia due to Alzheimer's disease (Early symptomatic Alzheimer's disease) who are apolipoprotein E ε4 (ApoE ε4) non-carriers with confirmed amyloid pathology (see section 4.4)."

The design of study AACI was conventional to assess efficacy of donanemab treatment, i.e., randomised double-blind placebo-controlled parallel group study with a duration of 76 weeks in 1736 patients. At week 24, 52 and 76 donanemab treated patients had a blind switch to placebo if amyloid reduction (on PET scan) was below a certain cut-off point (<11 centiloids or between 11 and 25 centiloids for 2 consecutive scans). This MAA includes efficacy data up to 76 weeks.

Phase 2 study AACG was a randomised, double-blind, placebo-controlled study in 272 patients with MCI due to AD and mild AD with an intermediate tau load. Overall, the design was comparable with

study AACI, except that patients with high tau were not enrolled and the donanemab dose could be reduced to 700mg or placebo at week 24 or 52.

Dose

The choice of dosage for the phase 3 study is sufficiently justified. In study AACD (phase 1b) single and multiple dosing were investigated. In studies AACG (phase 2) and AACI flat dosing was introduced based on a 70-kg individual. The dose regimen is further based on the rate of ARIA's after single doses of 40mg/kg. In the original protocol, patients in the donanemab group were planned to receive 1400 mgQ4W. 43 (5%) Patients were randomly assigned to this dose and received this dose at initial infusion. Because of higher-than-anticipated serious ARIA-E, a titration period of 700 mg for the first 3 doses was added by a protocol amendment. After titration the dose is 1400mg Q4W.

Study participants <-> Target population

Neither a clinical diagnosis of MCI due to AD or Mild AD, nor a CDR-score of 0.5-1 is required for entering the study. The applicant divides patients into a 'clinical' category based on their MMSE score at screening. It should be noted that in clinical practice, a diagnosis of MCI due to AD or (mild) AD will always be made in conjunction of neurological examination, neuropsychological assessment and, if available, imaging (MRI/ PET-scan) and lab values. The applicant justifies the lack of a clinical diagnosis with the argument that 96.7% of the participants had a CDR-G score of 0.5 or 1, which in clinical practice is consistent with MCI-AD or mild AD dementia. This is acceptable. From the indication it is clear that patients should have a have a clinical diagnosis of MCI due to AD or mild AD. The applicant's approach to not specify a range of tau load in the indication is agreed. Research shows that tau is more associated with cognition and clinal progression than amyloid is (Ossenkoppele, Brain, 2016; Hanseeuw, JAMA Neurology 2019). This is a valid argument to distinguish between low and medium tau load as the natural progression and as such treatment effects might differ between those groups. Language in the SmPC is proposed to allow for an individual B/R weighing by a physician. This is agreed. Another argument is that measuring tau pathology would be an (additional) complex implication, after that amyloid beta and APOE4 status (see rest of assessment) has to be determined. Based on the inclusion criteria also patients with other types of dementia like dementia with Lewy Bodies or patients with a clinical diagnose of subjective memory complaints (SMC) -regardless of underlying amyloid and to a lower extent tau pathology- could have been included. Differential diagnosis can be challenging, even with the availability of pathological markers. However, it is agreed that these markers can provide more certainty about the underlying pathology. It is unknown if at follow-up the diagnosis of patients were changed from MCI due to AD or mild AD into another (dementia) diagnosis.

Based on their tau deposition patients were divided into the intermediate tau population (patients with low–medium tau pathology) or overall population (also the patients with high tau pathology). Patients were screened for tau pathology as measured by tau PET scan at baseline (visual interpretation and quantification). Both measures were used for inclusion/exclusion in the low/medium tau population or high tau population. Patients with a negative visual assessment, or a visually assessed moderate tau pattern + quantitated as <1.1 were not included in the study. In contrast, patients with an advanced visual assessment and quantitated as <1.1 were included in the study. Although the visual reading could be negative, based on quantitative division this group showed measurable change from baseline on the ADAS-Cog and MMSE in a Phase 2/3 flortaucipir PET observational study and the tau PET sub-study of the Phase 3 solanezumab trial.

No patients with behavioural disturbances related to AD were included in the study. As such no conclusions of a possible effect of donanemab on behaviour can made.

Endpoints

In a protocol amendment the primary endpoint of the study was changed from the CDR-SB into the iADRS while the study was already ongoing. The iADRS is a composite endpoint of a cognitive and functional scale and was developed by the applicant. At the time of the CHMP SA this endpoint was at discussion since it was not fully validated. In the end the CHMP endorsed the iADRS as primary endpoint. Thus, (regulatory) experience with this scale is sparse. In the assessment much weight will be given to the CDR-SB, an established endpoint. Other endpoints are the ADAS-Cog13, ADCS-iADL and the MMSE. No outcomes assessing neuropsychiatric/ behavioural symptoms were included in the pivotal study. Therefore, a possible effect of donanemab on neuropsychiatric/ behavioural symptoms cannot be established.

Protocol amendments

Several protocol amendments were made for study AACI. The most important are the conversion from a phase 2 into a phase 3 study, subsequent changes in increasing the sample size, inclusion of p-tau as pre-screening assessment and the change in primary endpoint from CDR-SB to iADRS and change of the analysis method for the primary endpoint. When the protocol amendments were made less than 7% of patients was randomised. Because of the small number of patients involved and the blinding, the impact is considered limited.

Protocol deviations

About half of important protocol deviations was in study procedures compliance. 21.3% Of the important protocol violation concerned the inform consent. All patients provided informed consent before randomisation in the study. In addition, 9.6% of protocol deviations concerned the safety reporting. The majority of the safety reporting protocol violations were MRI missing or not performed per protocol or MRI not reviewed locally. For 80 patients on donanemab and 76 patients on placebo the MRI was missing or not performed. This is balanced between treatment arms. Also, in almost half of randomised patients (N=857; 49.4) there were protocol deviations for study procedure compliance. The protocol deviations are presented using a filtering algorithm that runs sequentially, meaning that if a patient had more than 1 protocol deviation this is only counted as one deviation, under the string that is first in the algorithm. This may lead to an underestimation of the number of total protocol deviations, immunogenicity-related protocol deviations, MRI-related protocol deviations, and protocol deviations related to the lead-in screening. A GCP inspection was conducted for the pivotal study AACI. After inspection of two sites (Poland and Canada) and the sponsor site, five major findings were reported. The deviations identified are not considered to impact the acceptability of the safety and efficacy data.

According to the protocol, a minimal number of Lilly personnel would see the randomisation table and treatment assignments before studies AACI and AACG were complete. An outline of the personnel that was unblinded because of the roles they had to perform is provided. Site personnel and patients remained blinded after completion of the study because of possible continuation in the long-term extension or safety follow-up.

There are three indications for poor study conduct: 1) the number of important protocol violations, 2) the inclusion of moderate AD patients, 3) the absence of (post)baseline values, with more missing data in the donanemab arms. This raises the question how well study conduct was monitored. These are potential triggers for inspection. Four study sites of the pivotal study and five sites of the phase 2 study have been inspected by the FDA. According to the applicant, none of the inspections are classified as official action indicated.

Methodology

Initial analyses were all performed in the evaluable efficacy population set (EES) rather than the intention-to-treat (ITT) population set. Restricting analyses to a subset with a post baseline measurements for the outcome available may have resulted in selection bias. Analyses methods further seem to assume that missing outcomes after discontinuation are missing at random. This assumption is unlikely to be satisfied. The percentage of participants that discontinue is non-negligible and seems to differ between the treatment arms. The statistical properties of the natural cubic spline model are yet unclear. Several analyses in the ITT using mixed model for repeated measures (MMRM) have been provided by the applicant. The estimates from these analyses in the ITT population using different strategies for imputation vary strongly between the different sensitivity analyses, which seems to suggest a strong dependence on how missing observations are handled (in the most conservative method, using worst observed change imputation for missing data after death and discontinuation due to ARIA event, results were not statistically significant for the primary endpoint or its components). Analyses using MMRM in the ITT population for the primary and all secondary endpoints that use a jump-to-reference imputation method for missing outcomes after ARIA events, death or permanent study discontinuations for other reasons are considered to yield the most realistic estimates. The results have been provided for this analysis strategy upon request.

Patients who experienced ARIA's were monitored more intensively with additional MRI. This may have impacted on the blinding. The applicant was requested to discuss the impact of the additional MRIs on the blinding. Furthermore, in patients who developed ARIA, depending on the investigators' decision, suspension, change in the dosing schedule or continuation of treatment could be applied. A clarification how changes in dosing in patients with ARIA impacted the treatment outcomes (both from the efficacy and safety perspectives) in subjects who developed ARIA was requested. Additional analyses show that censoring of observations after ARIA did not alter conclusions. Also, the majority of patients with ARIA seem to have at least some measurements after ARIA and a large number has 5 and 6 measurements.

Response based dosing

The applicant introduces an amyloid response-based dose adaptation. A blinded switch to placebo in the donanemab arm in those meeting threshold amyloid plaque reduction was an inherent part of the treatment strategy evaluated. Donanemab-treated patients are switched to placebo in a blinded manner during the study if they met either 1 of the 2 criteria at Week 24, 52, or 76: 1) amyloid level was <11 CL at any single amyloid PET scan, or 2) amyloid level was ≥11 to <25 CL in 2 consecutive amyloid PET scans, donanemab treated patients had a blind switch to placebo. Reaching the threshold of 24.1 centiloids implies a reduction of 75% in cerebral amyloid load. In case of no validated amyloid monitoring method it is recommended to stop treatment after 76 weeks. While it is acknowledged that at Week 76, approximately 74% participants in the intermediate tau population and 69% participants in the overall population showed a significant reduction in amyloid plaque and met the dose cessation criteria, the clear recommendation to stop the treatment after 78 weeks if amyloid evaluation is not available is not clear. It should be noted that 31% of subjects in the overall population did not meet the dose cessation criteria. Efficacy and safety in moderate-severe patients has not been investigated. Stopping rules are included in the SmPC, specifying that treatment should be stopped after 18 months of treatment, or earlier in case patients progress to the next (moderate) stage of the disease.

Efficacy data and additional analyses

Pivotal study – AACI (phase 3)

By further restricting the indication to APOE-E4 non-carriers only a sample of approximately 29% (N = 510) of the population studied in the pivotal study remains. This subsample is regarding demographics

generally comparable with the overall population including all APOE-E4 genotypes. Though, this sample is slightly older, the baseline cognitive measures are similar to the sample including all APOE E-4 genotypes.

A clear reduction in cerebral Aβ load as measured by the PET scan was found after treatment with donanemab. The calculation of the amyloid load was based on the centiloid method since two amyloid PET tracers were used. The centiloid method is applied for the first time in the context of a registrational study. Baseline values and data of SUVR change in six cortical regions (anterior cingulate, posterior cingulate, parietal, precuneus, temporal, medial orbitofrontal) are provided for the placebo- and donanemab groups in low-medium tau, high tau, and combined populations. A difference in amyloid reduction between placebo and donanemab in SUVR is visible in the three subgroups for each cortical region, with most amyloid reduction in the anterior cingulate and precuneus. These data indicate that a composite SUVR of the separate regions would show a difference between placebo and donanemab.

On the iADRS, in both the restricted (APOE-E4 non-carriers only) and overall (all APOE-E4 genotypes) populations, the mean change on the iADRS at week 76 was lower for the donanemab treated patients compared with placebo. On the CDR-SB, a difference between placebo and donanemab at week 76 was found in both the restricted and overall populations. On the ADAS-COG13 and ADCS-iADL, statistically significant differences between placebo and donanemab were found in the overall population, for the restricted population these were not statistically significant anymore.

The numbers of the participants in each of the EES sets are not found in the provided CSR. Numbers of patients included in the EES are provided for each outcome for the intermediate and overall population. At week 76, for around 20-25% of patients data is missing. Difference in proportion missing is especially large in the overall population.

Upon request subgroup analyses have been provided. These subgroup analyses indicate that APOE4 homozygous patients seem to benefit the least from treatment, and patients with middle third in screening tau SUVr benefit most. Results in the MCI group are more inconsistent than for the Mild AD group that consistently favours donanemab over placebo in the overall population.

Additional analyses were requested because of uncertainties that limited the interpretation of the data and the results both from an efficacy as well as a methodological perspective, the latter questioned the robustness of the data. These analyses showed that:

- The requested cumulative frequency plots for all randomised patients are provided. These indicate that at several cut-off points for different outcomes the difference between placebo and donanemab is 15% maximum for being a responder on a certain cut-off in the overall population, and 12% in the restricted population.

- 2x2 Tables displaying concordance between reaching MCID on iADRS (yes/no) versus reaching MCID on CDR-SB (yes/no) were provided. These indicate that overall, in both populations, the overlap between both ranges is approximately 70-75%. Except for the placebo group when MCI is defined based on the MMSE: then approximately 55% concordance between iADRS and CDR-SB is found. The concordance between these measures is considered slight to moderate.

- The applicant presents the results for the intermediate population (low-medium tau load) and the total population (low-medium-high tau load). As the intermediate population covered 69% of the overall population the results of the overall population are driven by that of the intermediate population. For a clear evaluation of effect modification based on tau pathology, results and analyses of the low tau group only as well as for the medium tau group only were requested. These are not provided. Subgroup analyses for iADRS and CDR-SB based on tau

load stratified in terciles (SUVr); <33, 33-67 and >76 terciles are provided. In the subgroup >67 tercile, the differences in change are less. These finding seems to imply that the greatest effect is seen when the tau load is not too high. The applicant indicates that the tau tercile analyses are exploratory and post-hoc, limiting conclusions. In the SmPC, language allowing a physician for an individual B/R is included.

- There are unclarities regarding the time to clinical worsening analyses. All are conducted in the EES and not in the ITT. Events are defined as a worse score as compared to baseline at two consecutive visits during the double-blinded phase. The estimates at 600 days strongly differ between the analysis as originally planned and the sensitivity analysis, as could be expected. Interpretation of these curves should be restricted to follow-up up to 480 days to minimize any impact of not confirming decreases at the 76 week visit. The several Kaplan-Meier curves show that in, both the restricted an overall population, differences between placebo and donanemab are small in terms of responders for different cut-offs; i.e., with a difference of maximum of 16% at t=480 in the overall population, and 12% in the restricted population. This may translate into certain % of lower risk progression, but in terms of absolute differences this is considered minimal.

Limited long-term efficacy data are available. Preliminary results from the LTE of study AACI were submitted at a very late stage of the evaluation procedure. As described above, there are several reasons why the interpretation of these high-over data is limited and as such no conclusions can be drawn. The final data are expected to be completed in Q3 2025.

Restricted indication

Because of safety reasons it is post-hoc proposed to restrict the indication further to APOE4 non-carrier patients. In the pivotal study 510 (29%) patients would represent the targeted population. In this more restricted population the effect sizes show some increase in both populations and when applying jump-to reference-imputation for missing data. Hazard ratios of progression in terms of points decline on outcome measures/ at the CDR-global in the restricted population are also provided. Although these show high ratio's with statistically significant differences, the absolute differences between placebo and donanemab (irrespective of the included population and imputation methods) are not so impressive. The absolute difference in number of responders (events) is for most comparisons around 10%.

Clinical relevance

This is the first study in AD with the iADRS as primary endpoint. This makes it hard to contextualise the findings. The difference between placebo and donanemab is statistically significant in the overall population, except for the most conservative imputation strategy. The LS mean change difference between placebo and donanemab is around 3 points after a time period of 18 months treatment on a scale ranging from 0-144 in the EES. In the restricted indication, applying MRMM with missings after ARIA AE or death imputed using a jump to reference method, the LS mean change difference between placebo and donanemab is around 2 points at 18 months after treatment initiation.

Wessels et al (2022) used an anchor based approach to determine the minimal clinically important difference (MCID) for patients with MCI due to AD and mild AD. An anchor was a CDR-SB increase of 1 point over a time period of 12 months for MCI due to AD and 2 points for mild AD and moderate-severe AD (based on the study by Lansdall 2023). Results suggest an iADRS MCID of 5 points for MCI due to AD and 9 points for AD with mild dementia in 1 year. Assuming linearity, an iADRS MCID of 5 points/year for MCI due to AD would translate into a difference of 7.5 points/18months. This 'threshold' is crossed by all placebo and donanemab groups in all populations (i.e., intermediate, overall and high), except for the donanemab group in the intermediate population. Similar, an iADRS

MCID of 9 points/year for mild AD would translate into a difference of 13.5 points/18months. This 'threshold' is crossed by the placebo and donanemab groups the high population.

There are several uncertainties regarding the MCID for the iADRS as described by Wessels et al (2022), 1) Currently, the literature that is available concerning the minimal clinically important difference (MCID) on the iADRS is published by employees of the applicant. Limiting an 'independent' source to validate or reflect on this MCID. 2) It Is not clear whether the MCID applies to groups (difference in means score) or whether it is responder based (relevant shift in an individual patient). 3) A clinician-based judgment of meaningful decline" or an anchor reflecting patient/care partner input regarding "meaningfulness" was missing in this study.

The CDR-SB is an established outcome in AD research. However, the MCID of the CDR-SB is also under discussion: what outcomes can be considered as clinically meaningful for clinical trial design and decision making? In the field and literature debate is ongoing regarding the minimally clinical important difference (MCID), while some favour slowing of disease in months or percentage difference, other favour the absolute differences on clinical outcomes. In this debate the difference between clinically meaningful changes for an individual patient and on a group level is postulated (Petersen et al., 2023).

The LS mean difference between placebo and donanemab is around -0.50 points in both the noncarriers and overall population at a time period of 18 months. Andrews et al. described an increase of 0.5 as a minimal change on the CDR-SB as a cut-off for 50%-70% of visits with meaningful decline. The MCID estimate for the CDR-SB for MCI due to AD was 1 and for mild AD 2. The author now clarified that within-patient change thresholds were not intended to assess the meaningfulness of differences between group-level changes over time and instead may be useful to illustrate meaningful within-patient progression over the course of a clinical trial via supplementary responder/progressor analyses (Petersen et al., 2023).

Anchor-based estimates for MCID were developed by Lansdall et al (2023). For the CDR-SB, an increase of 1 point in 12 months is proposed as a 'minimal deterioration' threshold within a patient and an increase of 2.5 points in 12 months is proposed as a 'moderate deterioration' threshold. Thus, a direct translation to differences on a group level is limited. This hampers the interpretation of the results on group level on the CDR-SB.

Taking the %change after 76 weeks on both the ADAS-Cog13 and ADCS-iADL into consideration, it seems that the effect on the iADRS is mostly driven by the functional component, i.e. ADCS-iADL. The CDR-SB also consists of a functional and cognitive subscale. A domain analysis shows that the result on the overall composite score of the CRD-SB is not dominated by one dimension of the scale in both the low-medium and overall tau population. For the iADRS an analysis is provided that, according to the applicant, would allow for determination of a possible effect on this scale would be driven by one of the dimensions of the subscales. The figure provided does not allow for conclusions.

Responder analyses are of relevance for interpretation of the clinical relevance of the effect. As discussed before, the absolute differences in responders for various outcomes in the overall or restricted indications are considered small. For example, any increase on the CDR-global (defined as any increase, either for 2 consecutive visits or if a single increase at the week 76 visit; from 0.5 to 1 or from 1 to 2) is 45% for placebo and 35.5% for donanemab at 18 months after treatment initiation in the restricted population. This means that the absolute difference is 9.5%, which is small. Moreover, most patients in both placebo and donanemab treated arms do not progress in terms of shifting to the next clinical stage at the end of the double-blind placebo-controlled phase

Taking this altogether, it is hard to decide on the possible clinical relevance of the small effects in this single pivotal study.

High tau only population

In the high tau only population there is no difference between the donanemab treated group and the group on placebo on the iADRS, CDR-SB, ADCS-iADL and ADAS-Cog 13 despite a comparable amyloid reduction as in the restricted population.

The applicant concludes that patients irrespective of tau burden have benefit of donanemab treatment. This position is not shared given these analyses in the high tau group. This seems to imply that patients with higher tau levels are too advanced to obtain an effect donanemab, or an indication of no downstream effect of donanemab on tau. The SmPC includes text regarding these findings so to that physicians can make an individual B/R weighing.

Concomitant medication

In total, 61% of the patients used cholinesterase inhibitors and/or memantine at baseline. In addition, dose adjustments or initiating cholinesterase inhibitors and/or memantine were made during the study in 17.8% of patients on placebo and 11.3 of the patients on donanemab. With 12.1% of placebo-treated patients and 8.1% of donanemab-treated patients initiated new symptomatic AD medications during the study. Overall, there seems to be no confounding effect of concomitant AD medication.

Considering high proportion of patients with anxiety/depression (44.5% vs 47.2 in placebo and donanemab groups, respectively), overall, the utilisation of antidepressants/anxiolytics was balanced between both groups. A limited number of patients used antipsychotics. The use of antipsychotics was overall well balanced between both groups, with an exception of quetiapine. However, it is not to be expected that the use of quetiapine could have affected the study results.

Supportive study – AACG (phase 2)

Supportive Phase 2 Study AACG (TRAILBLAZER-ALZ) was a double-blind, placebo-controlled, study to evaluate the safety and efficacy of donanemab in patients with early symptomatic AD (prodromal AD and mild dementia due to AD), to assess whether removal of existing amyloid plaque can slow the progression of disease as assessed by clinical measures and biomarkers of disease pathology and neurodegeneration over up to 72 weeks of treatment, followed by final study assessments at 76 weeks. The overall study design is considered acceptable for an exploratory study. Amyloid beta load decreased after donanemab treatment and this was notable at 24 weeks (first PET scan after baseline). However, no statistically significant difference was reported in change from baseline to Week 76 in global tau load. On the primary endpoint iADRS and on the ADAS-Cog13 (one of the two subscales of the iADRS), difference between placebo and donanemab was found. This implies that the effect found on the iADRS is mainly driven by the effect on the ADAS-COG13. However, on the CDR-SB, ADCS-iADL and MMSE there was no difference between placebo and donanemab and thus did not support the primary endpoint. Thus, the results of the phase 2 study are less consistent in the intermediate tau population than the results in this population of the phase 3 study. This makes this study of limited support for the single pivotal phase 3 study.

Single pivotal study

In the case of a single pivotal trial, the data have to be particularly compelling with respect to internal and external validity, clinical relevance, statistical significance, data quality, and internal consistency (points to consider on application with 1. Meta-analysis, 2. One pivotal study, EMA; PMP/EWP/2330/99). Whereas in this point to consider it is stated that there is no formal requirement to include two or more pivotal studies in the phase 3 programme it is also stated that there are many reasons why it is usually prudent to plan for more than one study in the phase 3 programme. These include among others a new pharmacological principle, phase 1 and phase 2 data that are limited or unconvincing and a therapeutic area with a history of failed studies. This latter aspect particularly

applies to AD and agents the based on the amyloid hypothesis which has a history of many failed studies. Relying on one pivotal study has a risk of false positive conclusions. The aducanumab dossier illustrates this. Here after a promising phase 2 study two identical pivotal phase 3 studies were performed. Whereas both studies showed a clear and similar reduction in amyloid load compared to placebo, with respect to the clinical outcome (CDR-SB) one study was positive, with questionable clinical relevance, but the other was clearly negative. Which study would represent the true treatment effect could not be determined. Hence there is a particularly strong need to have a clear demonstration that targeting existing amyloid plaques can delay the progressive disease course of AD. Relying on one pivotal study has a risk of false positive conclusions. In addition, multiple modifications were made while the study AACI was ongoing, this may have affected study integrity.

2.6.7. Conclusions on the clinical efficacy

This MAA contains a single pivotal study with no efficacy data after 76 weeks. There remain uncertainties on the clinical meaningfulness of the small effects of donanemab, also on the long term. This should be seen in the context of the benefit-risk discussed below.

2.6.8. Clinical safety

- ***Patient exposure***

The donanemab clinical programme includes eight clinical studies in Alzheimer's disease (AD), of which two are phase 1(b) studies and six are phase 2 or phase 3 studies.

The focus of the safety assessment in this assessment report lies on the randomized, placebo-controlled, double-blind single pivotal phase 3 study AACI in patients (n=853 donanemab, n=874 placebo) with MCI due to AD and mild AD dementia (hereafter referred to as "AACI-PC").

Results will be held against an integrated safety set (hereafter referred to as "All Dona"; n=2727), consisting of AACI-PC plus the following studies:

- randomized, placebo-controlled, double-blind phase 2 study AACG
- double-blind extension period that is part of phase 3 study AACI (AACI-LTE)
- open-label study that is part of phase 3 study AACI, new patients (AACI-Safety Addendum)
- extension study for "control group" completers of phase 2 study AACG (Study AACH), and
- active comparator phase 3 study with donanemab and aducanumab (Study AACN).

Participants on donanemab or placebo, who received at least one dose of study treatment were eligible for inclusion in the safety sets. Patients were followed from first dose of treatment to end of treatment period + 57 days, or the day prior to the first LTE visit, whichever occurred first (if applicable).

AACQ

In response to the safety concerns raised in the D180 AR, preliminary safety results of an ongoing phase 3b study (AACQ) were submitted. In AACQ, the effect of different dosing regimens on ARIA incidence and amyloid lowering was investigated. Data up to Week 52 are currently available.

AACI-PC

In AACI-PC, 713/853 (83.6%) of patients received donanemab at the recommended dose (i.e., 3 x 700 mg Q4W, 1400 Q4W thereafter). In AACI-PC, 510 of 853 patients (59.8%) in the donanemab group were exposed to donanemab for at least 12 months; 174 patients (20.4%) were exposed for at least 72 weeks. This was not necessarily at the recommended dose (i.e., three infusions of 700 mg donanemab Q4W and then 1400 mg Q4W).

More placebo-treated patients than donanemab-treated patients completed the study (79.7% vs. 72.3%, resp.) and continued in the LTE study (76.9% vs. 67.9%, resp.). Treatment discontinuation was higher under donanemab (29.3%) compared to controls (20.1%). This difference is mostly driven by withdrawal due to AEs (11.4% donanemab, 3.2% placebo). This does not include withdrawals due to death (1.6% donanemab, 1.0% placebo), which could also be considered a TEAE. Discontinuations for which reasons were not further specified (e.g., 'physician decision' or 'lost to follow-up') were also assessed by the applicant for possible AE-driven withdrawals.

In general, patient demographics, baseline (disease) characteristics (including APOE status), and concomitant medications (including antithrombotic use), were similar between the treatment groups. Use of non-aspirin antiplatelets was higher in the donanemab group (n = 52, 6.1%) compared with the placebo group (n = 33, 3.8%). The most commonly used antithrombotic in both groups was aspirin.

All Dona

So far, more than 2700 subjects have been exposed to donanemab; of which 964 patients have been exposed to donanemab at the recommended dose for at least 12 months (i.e., at least 12 infusions of donanemab with no more than three infusions of 700 mg followed by at least 9 infusions of 1400 mg), and 215 patients have exposure data at the recommended dose up to 76 weeks.

- ***Adverse events***

AACI-PC

The TEAEs for the AACI-PC period were defined as events that occurred prior to either the first visit date of LTE or end of the placebo-controlled phase + 57 days, whichever occurred first. Table 20 provides an overview of TEAEs in AACI-PC an All Dona.

Table 20. Overview of adverse events, AACI-PC and All Dona

	AACI-PC		**All Dona**
	Placebo (N = 874) n	**Donanemab (N = 853) n**	**N = 2727 n**
Deaths	10 (1.1%)	16 (1.9%)	32 (1.2%)
Serious adverse events	138 (15.8%)	148 (17.4%)	411 (15.1%)
Discontinuation of study due to AE	32 (3.7%)	69 (8.1%)	158 (5.8%)
Discontinuation of treatment due to AE	38 (4.3%)	112 (13.1%)	265 (9.7%)
TEAEs	718 (82.2%)	759 (89.0%)	2129 (78.1%)
TEAEs related to treatment by investigator	173 (19.8%)	410 (48.1%)	1063 (39%)

Made by the assessor. Source: Table AACI.8.2 and AACI.8.174 of CSR of AACI, Table 2.7.4.12. of Summary of clinical safety, Table APP.2.7.4.7.A-10. of Appendix of Summ. of clinical safety. Abbreviations: AE = adverse event; SAE = serious adverse event; TEAE = treatment-emergent adverse event.

Common treatment-emergent adverse events

AACI-PC

In Table 21, TEAEs reported in ≥2% of patients in AACI-PC by PT in order of decreasing frequency are presented.

Common TEAEs that occurred more often under donanemab than in controls were ARIA-E (24.0% donanemab vs. 1.9% placebo), ARIA-H (19.7% donanemab vs. 7.4% placebo), superficial siderosis of CNS (6.8% donanemab vs. 1.1% placebo), infusion-related reaction (IRR; 8.7% donanemab vs. 0.5% placebo), headache (14.0% donanemab vs. 9.8% placebo).

Table 21. Summary of Treatment-Emergent Adverse Events Preferred Term in ≥2% of Subjects by Decreasing Frequency within System Organ Class, AACI-PC

	Placebo (N=874)		LY3002813 (N=853)		Total (N=1727)	
Preferred Term	n	(%)	n	(%)	n	(%)
COVID-19	154	(17.6)	136	(15.9)	290	(16.8)
Amyloid related imaging abnormality-microhaemorrhages and haemosiderin deposits	65	(7.4)	168	(19.7)	233	(13.5)
Fall	110	(12.6)	114	(13.4)	224	(13.0)
Amyloid related imaging abnormality-oedema/effusion	17	(1.9)	205	(24.0)	222	(12.9)
Headache	86	(9.8)	119	(14.0)	205	(11.9)
Urinary tract infection	59	(6.8)	45	(5.3)	104	(6.0)
Dizziness	48	(5.5)	53	(6.2)	101	(5.8)
Diarrhoea	50	(5.7)	43	(5.0)	93	(5.4)
Arthralgia	42	(4.8)	49	(5.7)	91	(5.3)
Fatigue	45	(5.1)	42	(4.9)	87	(5.0)
Infusion related reaction	4	(0.5)	74	(8.7)	78	(4.5)
Anxiety	41	(4.7)	35	(4.1)	76	(4.4)
Hypertension	40	(4.6)	36	(4.2)	76	(4.4)
Back pain	38	(4.3)	34	(4.0)	72	(4.2)
Nausea	34	(3.9)	37	(4.3)	71	(4.1)
Superficial siderosis of central nervous system	10	(1.1)	58	(6.8)	68	(3.9)
Contusion	32	(3.7)	35	(4.1)	67	(3.9)
Upper respiratory tract infection	38	(4.3)	26	(3.0)	64	(3.7)
Depression	28	(3.2)	33	(3.9)	61	(3.5)
Nasopharyngitis	26	(3.0)	27	(3.2)	53	(3.1)
Skin laceration	23	(2.6)	28	(3.3)	51	(3.0)
Vomiting	24	(2.7)	27	(3.2)	51	(3.0)
Syncope	24	(2.7)	26	(3.0)	50	(2.9)
Cough	28	(3.2)	18	(2.1)	46	(2.7)
Confusional state	23	(2.6)	21	(2.5)	44	(2.5)
Pain in extremity	20	(2.3)	20	(2.3)	40	(2.3)
Agitation	21	(2.4)	17	(2.0)	38	(2.2)
Asthenia	16	(1.8)	20	(2.3)	36	(2.1)
Constipation	20	(2.3)	16	(1.9)	36	(2.1)

Abbreviations: N = number of subjects in the analysis population; n = number of subjects with events meeting specified criteria. *a - p value for overall treatment effect were computed using Fisher's Exact test. Treatment-emergent adverse event (TEAE) is defined as an event that first occurred or worsened after the treatment initiation date and up to either the first visit date of long term extension phase (LTE) - 1 day or end of treatment period in double blinded phase + 57 days, whichever occurs first.

All Dona

The frequency of common TEAEs under donanemab and the frequencies per SOC were slightly lower than in the placebo-controlled setting.

Adverse drug reactions for labelling

The following adverse drug reactions (ADRs) were identified for inclusion in section 4.8 of the SmPC: ARIA-E, ARIA-H and headache (very common ADRs); IRR, nausea, and vomiting (common ADRs); and anaphylactic reaction (uncommon ADR). The ADRs are summarized in Table 22.

Events were determined as ADRs by the applicant based on strength of the association with donanemab treatment assessed using pre-defined core safety information screening criteria, biologic plausibility for a donanemab effect, clinical importance, and medical judgement.

Table 22. Frequency of adverse drug reactions, AACI-PC

System Organ Class (SOC) Preferred Term (PT)	**Placebo (N=874)** n	**Donanemab (N=853)** n
Gastrointestinal disorders		
Nausea	34 (3.9%)	37 (4.3%)
Vomiting	24 (2.7%)	27 (3.2%)
Injury, poisoning and procedural complications		
Infusion-related reaction	4 (0.5%)	74 (8.7%)
Anaphylactic reaction	0	3 (0.4%)
Nervous system disorders		
ARIA-E[a]	18 (2.1%)	205 (24.0%)
ARIA-H[a,b]	119 (13.6%)	268 (31.4%)
Headache	86 (9.8%)	119 (14.0%)

Made by the assessor. Abbreviations; ARIA-E = amyloid-related imaging abnormalities-oedema/effusions (also known as vasogenic oedema); ARAIA-H = amyloid-related imaging abnormalities-haemorrhage/hemosiderin depositing (including brain microhaemorrhage and superficial siderosis); MRI = magnetic resonance imaging. a = assessed by MRI or TEAE cluster. b = includes cerebral microhaemorrhage and superficial siderosis. Source: Table AACI.5.24. and Table AACI.5.28. of CSR AACI.

Severe treatment-emergent adverse events

AACI-PC

Severe TEAEs were observed more often under donanemab (12.0%) than in control patients (8.9%). TEAEs by maximum severity are summarized in Table 23.

Severe TEAEs that occurred more under donanemab than in controls included ARIA-E (1.6% donanemab vs. 0% controls), ARIA-H (0.6% donanemab vs. 0% controls), Fall (0.6% vs. 0.2%), infusion-related reaction (0.4% vs. 0%), and agitation (0.4% vs. 0.1%).

Table 23. Summary of TEAEs by maximum severity, AACI-PC

Severity	**Placebo (N = 874) n (%)**	**Donanemab (N = 853) n (%)**	**Total (N = 1727) n (%)**
Participants with ≥1 TEAE	718 (82.2)	759 (89.0)	1477 (85.5)
Mild	322 (36.8)	306 (35.9)	628 (36.4)
Moderate	318 (36.4)	351 (41.1)	669 (38.7)
Severe	78 (8.9)	102 (12.0)	180 (10.4)

Source: Table AACI.8.176

All Dona

A similar pattern of severe AEs under donanemab was observed. Severe TEAEs that occurred ≥ 1% of patients included ARIA-E (1.5%).

- ***Serious adverse events, deaths, and other significant events***

Serious adverse events

AACI-PC

Serious adverse events occurred in more often in patients treated with donanemab (17.4%) compared to control patients (15.8%). The disbalance in SAEs between placebo and donanemab was mainly reported in the SOC of Nervous system disorders (4.7% donanemab vs. 3.2% controls), and driven by events of ARIA-E (1.5%) and ARIA-H (0.5%). No serious ARIAs were observed in the control group.

The most commonly reported SAEs by PT (those occurring in ≥1% of donanemab-treated patients) are summarized in Table 24.

Table 24. Serious adverse events occurring in ≥1% of donanemab-treated participants (AACI-PC), by preferred terms within system organ class while on treatment

SAE	Placebo (N = 874) n (%)	Donanemab (N = 853) n (%)
Participants with ≥1 SAE	138 (15.8)	148 (17.4)
Syncope	13 (1.5)	9 (1.1)
ARIA-E	0	13 (1.5)
COVID-19	4 (0.5)	9 (1.1)

Abbreviations: ARIA-E = amyloid-related imaging abnormalities–edema/effusions (also known as vasogenic edema); COVID-19 = coronavirus disease 2019; N = number of participants in the analysis population; n = number of participants in the specified category; PC = placebo-controlled; SAE = serious adverse event.
Source: Table AACI.8.178

SAEs of special interest included:

- ARIA-E (1.5% donanemab vs. 0% placebo);
- ARIA-H (0.5% donanemab vs. 0% placebo);
- A macrohaemorrhage event of haemorrhagic stroke (0.1% donanemab vs. 0.1% placebo).
- Based on the narrow search terms, 0.4% donanemab-treated participants and 0.1% placebo-treated participants were reported to have at least 1 serious hypersensitivity or IRR event.

All Dona

A total of 411 (15.1%) donanemab-treated participants reported one or more SAEs. The frequency and types of SAEs were similar to AACI-PC (ARIA-E: 1.0%, syncope 0.9%, Covid-19: 0.7%). ARIA-E was the most frequently reported SAE in both safety sets.

Deaths

AACI-PC

More donanemab-treated patients died than control patients (1.9% [n = 16] vs. 1.1% [n = 10], respectively). Of the deaths in the donanemab group, three were deemed related to donanemab by the investigator:

- one participant died due to ARIA-E;
- one participant died due to ARIA-H (also with haemorrhagic stroke reported as a cause of death in the narrative, with final diagnosis of ARIA-H);
- the third participant had SAEs of ARIA-E and ARIA-H, was admitted to hospice and died.

All Dona

An additional 15 deaths other than those reported in donanemab-treated patients in the placebo-controlled studies were reported (n=32, 1.2%).

One additional death (symptomatic ARIA-E) in a donanemab-treated participant was reported after the database lock.

Beyond the three ARIA-associated deaths, no clear association of fatal SAEs with donanemab treatment was identified by the applicant.

The assessors note that some fatal cerebral or intracranial haemorrhages were also associated with donanemab treatment. As these are not summarized by the applicant, they are presented below:

- One fatal thalamic haemorrhage was considered related to donanemab treatment by the investigator.
- One death was attributed to serious ARIA-H (see above), but the patient died following a sequence of events (from mild ARIA-E to severe ARIA-H) resulting in fatal severe cerebral haemorrhage and haemorrhagic stroke;
- In one fatal case, death was attributed to ischaemic stroke, but the patient died after multiple intracranial haemorrhages. In the opinion of the study investigator, "the presenting CVA was not related to the study drug, but the resulting haemorrhages from tenecteplase (reported as tissue plasminogen activator [tPA]) could have been made worse by cerebral amyloid angiopathy and amyloid removed by blinded study drug".

Adverse events of special interest

As pre-specified in the AACI protocol, AEs of special interest (AESI) for donanemab were:

- ARIA and intracerebral haemorrhage >1 cm, and
- Hypersensitivity, anaphylaxis, and infusion-related reactions.

ARIA

ARIA was identified as an AE of special interest as it was known to occur with anti-amyloid monoclonal antibodies. The donanemab clinical development programme used risk mitigation steps to reduce the risk of ARIA-related poor outcomes:

ARIA-E and ARIA-H, including macrohaemorrhages, were managed in the clinical programme by excluding patients with pre-existing ARIA-E, >4 microhaemorrhages, >1 area of superficial siderosis, any macrohaemorrhage, or severe white matter disease. A dose titration regimen was used with an initial 3 doses of 700 mg Q4W before increasing to the full study dose of 1400 mg, and routine MRI scans per protocol schedule of activities were conducted. In the event of ARIA on MRI, the investigator could temporarily withhold IP, permanently discontinue IP, or continue to treat. For all new observations of ARIA - whether IP was continued, temporarily withheld, or permanently discontinued - an MRI was repeated every 4 to 6 weeks until resolution of ARIA-E or stabilisation of ARIA-H was documented.

AACI-PC

An overview of all ARIA events based on MRI and TEAE cluster during the AACI-PC period is provided in Table 25.

The incidence of any ARIA was higher in donanemab-treated participants (37%) than placebo-treated participants (15%). A total of 14 (1.6%) donanemab-treated participants reported SAEs that were attributable to any ARIA. No SAEs of ARIA were reported in the placebo group.

A total of 3 (0.4%) donanemab-treated participants and 2 (0.2%) placebo-treated participants reported macro-haemorrhage events. One participant from each treatment group reported 1 serious macro-haemorrhage event.

Table 25. ARIA overview, AACI-PC

ARIA Events	Placebo N = 874 n (%)	Donanemab N = 853 n (%)
Any ARIA (either -E or -H) based on MRI or TEAE cluster	130 (14.9)	314 (36.8)
Any SAE of ARIA based on TEAE cluster	0	14 (1.6)
ARIA-E based on MRI or TEAE cluster	18 (2.1)	205 (24.0)
Asymptomatic	17 (1.9)	153 (17.9)
Symptomatic	1 (0.1)[a]	52 (6.1)
SAE of ARIA-E based on TEAE cluster	0	13 (1.5)
Amyloid-related imaging abnormality–edema/effusion	0	13 (1.5)
ARIA-H based on MRI or TEAE cluster	119 (13.6)	268 (31.4)
SAE of ARIA-H based on TEAE cluster	0	4 (0.5)
SAE of ARIA-H in participants without SAE of ARIA-E	0	1 (0.1)
Amyloid-related imaging abnormality–microhemorrhages and hemosiderin deposits	0	1 (0.1)
SAE of ARIA-H in participants with SAE of ARIA-E	0	3 (0.4)
Amyloid-related imaging abnormality–microhemorrhages and hemosiderin deposits	0	3 (0.4)
Macrohemorrhage based on MRI or TEAE cluster	2 (0.2)	3 (0.4)
SAE of Macrohemorrhage based on TEAE cluster	1 (0.1)	1 (0.1)
Hemorrhagic stroke	1 (0.1)	1 (0.1)

Abbreviations: ARIA = amyloid-related imaging abnormalities; ARIA-E = amyloid-related imaging abnormalities–edema/effusions (also known as vasogenic edema); ARIA-H = amyloid-related imaging abnormalities–hemorrhage/hemosiderin deposition (including brain microhemorrhage and superficial siderosis); LTE = long-term extension; MRI = magnetic resonance imaging; N = number of participants in the analysis population; n = number of participants within the specified category; PC = placebo-controlled; SAE = serious adverse event; TEAE = treatment-emergent adverse event.

[a] One placebo-treated participant had ARIA-E during the AACI-PC period; however, the participant developed symptoms during the LTE period.

Source: Table AACI.8.182

ARIA-E

AACI-PC

ARIA-E incidence and symptoms

The incidence of ARIA-E based on MRI or TEAE cluster was higher in the donanemab group (n = 205; 24%) compared with the placebo group (n = 18, 2.1%) during the AACI-PC period. A total of 52 of 205 (25.4%) donanemab-treated participants with ARIA-E were reported as symptomatic. The most commonly reported symptoms (≥0.5% participants treated with donanemab) associated with ARIA-E were headache, confusional state, dizziness, nausea, and seizure. In part of the patients, symptoms did not resolve (e.g., seizure, aphasia).

ARIA-E onset and resolution (MRI)

The cumulative percentage of participants with ARIA-E experiencing the first ARIA-E event by donanemab infusion number ranged from 4.95% after receiving up to 1 infusion to 64.9% after receiving up to 5 infusions, and 100% after receiving up to 14 infusions. All patients with ARIA-E experienced their first serious ARIA-E event after receiving up to 5 infusions.

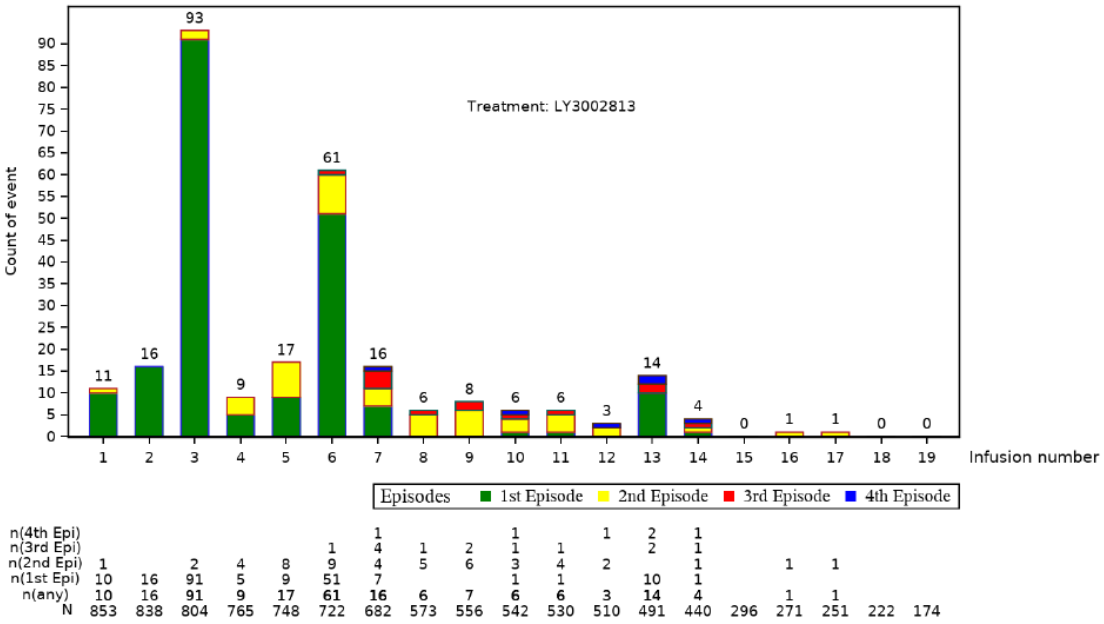
Based on MRI, 98.0% first ARIA-E episodes had complete resolution, with a median time to resolution of 58.0 days and a mean time to resolution of 72.4 days.

ARIA-E recurrence

Approximately 6% of donanemab-treated participants experienced multiple episodes of ARIA-E; 38 (4.5%) with 2 episodes and 13 (1.5%) with 3 or 4 episodes of ARIA-E during the AACI-PC period.

The figure below presents a histogram of onset of ARIA-E, initial and recurrent episodes, by infusion and based on safety MRI, in donanemab-treated participants in Study AACI-PC.

Figure 12. Histogram of onset of ARIA-E based on safety MRI by donanemab infusion number study AACI-PC, donanemab only



Abbreviations: ARIA-E = amyloid-related imaging abnormality-oedema or effusions (also known as vasogenic oedema); MRI = magnetic resonance imaging; n = number of subjects with onset of ARIA-E after the specified infusion and prior to or at any following infusions; If a patient has more than one episode after an infusion and prior to a subsequent infusion, the applicable episodes will be attributed to that infusion; N = number of subjects observed at the specified Donanemab infusion number; ARIA episodes are counted toward the closest infusion before the episode start; PC = placebo controlled.

ARIA-E severity (MRI), seriousness, deaths

The radiographic severity classification of ARIA-E is provided in Table 26.

Table 26. Radiographic severity classification of ARIA-E

Radiographic Severity	ARIA-E Extent
0 (no ARIA-E)	Absence of FLAIR hyperintensity suggestive of ARIA-E
1 (mild)	Mild FLAIR hyperintensity confined to sulcus and/or cortex/subcortex white matter (with or without gyral swelling and sulcal effacement), which affects an area of less than 5 cm in a single greatest dimension. Only a single region of involvement detected.
2 (mild+)	Mild presentation (see 1) in more than 1 site of involvement.
3 (moderate)	Moderate involvement (area of FLAIR hyperintensity measuring 5–10 cm in single greatest dimensions). Only a single region of involvement detected.
4 (moderate+)	Moderate involvement (area of FLAIR hyperintensity measuring 5–10 cm in single greatest dimensions) in more than 1 site of involvement, each measuring less than 10 cm in a single greatest dimension.
5 (severe)	Severe involvement (area of FLAIR hyperintensity measuring greater than 10 cm in single greatest dimension (white matter and/or sulcal involvement with associated gyral swelling and sulcal effacement)). One or more separate/independent sites of involvement may be noted.

The 5-point scale was converted to the 3-point scale for ARIA-E outputs using severities of mild, moderate, or severe (Bracoud et al. 2017). Based on the 3-point scale, the maximum severity of ARIA-E was mild (n = 58, 28.7%) or moderate (n = 130; 64.4%) in most participants in the donanemab group who had ARIA-E. Fourteen participants with ARIA-E (6.9%) had severe ARIA-E events.

Serious ARIA-E occurred in 13 (1.5%) participants treated with donanemab. Of these, most were heterozygous ε4 carriers (n = 8; 61.5%), 4 (30.8%) were ε4 homozygous carriers, and 1 (7.7%) was a non-carrier.

Twelve of the 13 participants with serious ARIA-E reported symptoms. Of the 12, 8 had resolution of symptoms during the AACI-PC period (6 had radiographic resolution and 2 did not have any post-baseline MRI data available), 2 were ongoing during the AACI-PC period and both had radiographic resolution, and 2 participants subsequently died. The asymptomatic ARIA-E SAE had radiographic resolution during the AACI-PC period.

During the AACI-PC period, 2 participants with SAEs of ARIA-E subsequently died.

Supportive treatment of ARIA-E (integrated safety pool AACG + AACI)

Most serious and/or symptomatic ARIA-E events were treated with supportive treatment. Among donanemab-treated participants who received medication to treat ARIA-E, approximately 60% received steroids. In general, medications used to treat ARIA-E include steroids, paracetamol, and ibuprofen.

Treatment discontinuation due to ARIA-E

The incidence of participants in the donanemab group who discontinued treatment due to any AE of ARIA-E (n = 21; 2.5%) was higher compared with those in the placebo group (n = 3; 0.3%).

<u>All Dona</u>

ARIA-E (MRI) was observed in 19.3% of participants. Serious ARIA-E occurred in 1.0% of donanemab-treated participants. Most serious ARIA occurred early in the treatment period. A total of three donanemab-treated participants reported serious ARIA and subsequently died. Nearly all serious ARIA was symptomatic. The frequency of symptomatic ARIA-E was 4.3%. Clinical symptoms associated with symptomatic and serious ARIA observed in All Dona were consistent with those reported in the placebo-controlled studies.

ARIA-H

AACI-PC

Incidence

The incidence of ARIA-H based on MRI or TEAE cluster was higher in the donanemab group (n = 268, 31.4%) compared with the placebo group (n = 119, 13.6%) during the AACI-PC period.

Symptoms of ARIA-H were not systematically collected, as they were difficult to distinguish from ARIA-E when ARIA-E and ARIA-H co-occur.

A total of four (0.5%) donanemab-treated participants had an SAE of ARIA-H, of which 3 (0.4%) participants also had an SAE of ARIA-E.

The incidence of macro-haemorrhage based on MRI or TEAE cluster (PTs: cerebral haemorrhage, haemorrhagic stroke) was 0.4% in the donanemab group and 0.2% in the placebo group.

The assessors note that there are other PTs that concern cerebral or intracranial haemorrhage, e.g.,:

- Subdural haematoma: placebo (0.1%); donanemab (0.5%)
- Cerebrovascular accident: placebo (0.1%); donanemab (0.2%)
- Cerebral haemorrhage: placebo (0.1%); donanemab (0.2%)
- Subarachnoid haemorrhage: placebo (0.1%); donanemab (0.2%)

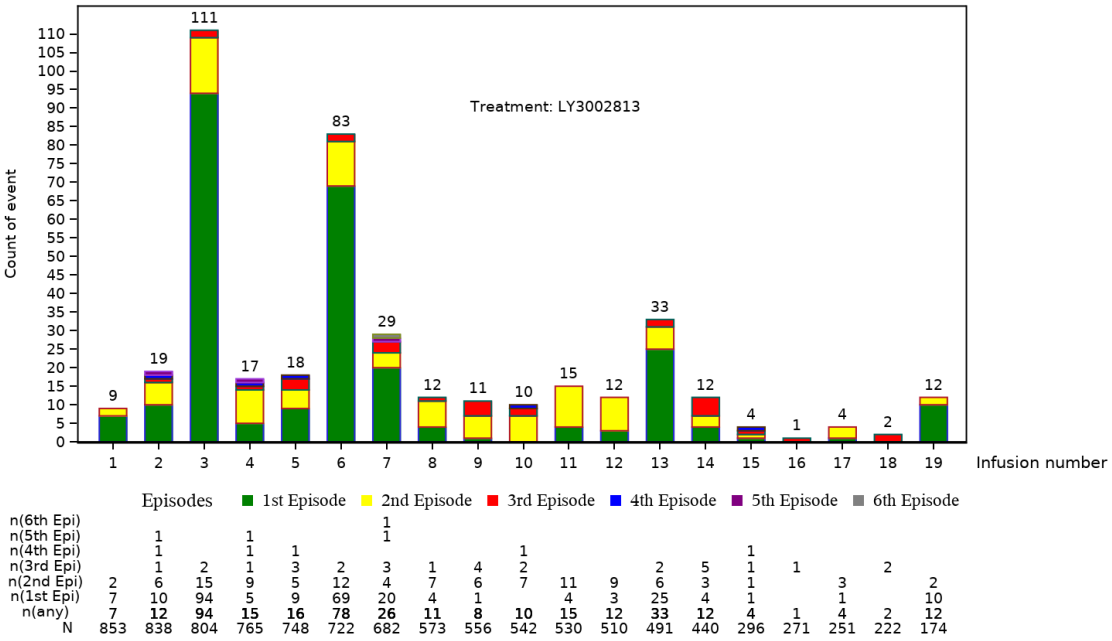
Based on extended search criteria for intracranial-haemorrhage (TEAE or MRI), 11 [1.3%] donanemab-treated participants had a (macro) haemorrhagic lesion versus 7 [0.8%] of placebo-treated participants. In All Dona, incidence of intracranial-haemorrhage was also 1.3%.

ARIA-H over time

Similar to ARIA-E, most of the first ARIA-H episodes occurred by the sixth infusion (within 24 weeks). However, the second episodes occurred all throughout treatment and third, fourth, and even fifth recurrences were observed earlier in treatment.

Figure 13 below presents a histogram of onset of ARIA-H, initial and recurrent episodes, by infusion and based on safety MRI, in donanemab-treated participants in Study AACI-PC.

Figure 13. Histogram of onset of ARIA-H based on safety MRI by donanemab infusion number study AACI-PC, donanemab only



Abbreviations: ARIA-H = amyloid-related imaging abnormality-haemorrhage or haemosiderin deposition (including cerebral microhaemorrhage and superficial siderosis); MRI = magnetic resonance imaging; n = number of subjects with onset of ARIA-H after the specified infusion and prior to or at any following infusions; If a patient has more than one episode after an infusion and prior to a subsequent infusion, the applicable episodes will be attributed to that infusion; N = number of subjects observed at the specified Donanemab infusion number; ARIA episodes are counted toward the closest infusion before the episode start; PC = placebo controlled.

ARIA-H severity

On the basis of radiographic severity, ARIA-H is categorized as mild, moderate, and severe based on the radiographic severity classification (refer to Table 27).

Table 27. Radiographic severity classification of ARIA-H

ARIA-H Type	Radiographic Severity		
	Mild	Moderate	Severe
ARIA-H microhemorrhage	≤4 treatment-emergent total microhemorrhages and new incident microhemorrhages	5–9 treatment-emergent total microhemorrhages or new incident microhemorrhages, whichever is greater	≥10 treatment-emergent total microhemorrhages or new incident microhemorrhages, whichever is greater
ARIA-H superficial siderosis	1 new or increased focal area of superficial siderosis	2 new or increased focal areas of superficial siderosis	>2 new or increased focal areas of superficial siderosis

Abbreviations: ARIA-H = amyloid-related imaging abnormalities – hemorrhage/hemosiderin deposition (including brain microhemorrhage and superficial siderosis).

The radiographic severity of ARIA-H events are as follows:

- ARIA-H: mild (n = 126/267; 47.2%), moderate (n = 52/267; 19.5%), and severe (n = 89/267; 33.3%);

- ARIA-H microhaemorrhage: mild (n = 140/220; 63.6%), moderate (n = 32/220; 14.5%), and severe (n = 48/220; 21.8%), and;
- ARIA-H superficial siderosis: mild (n = 44/134; 32.8%), moderate (n = 36/134; 26.9%), and severe (n = 54/134; 40.3%).

Serious ARIA-H and macro-haemorrhage, deaths

Serious ARIA-H occurred in four (0.5%) donanemab-treated participants. Three of the four serious ARIA-H events were severe and one was mild:

- One participant APOE genotype ε3ε3, died due to severe SAE of ARIA-H during the AACI-PC period.
- The second participant , APOE genotype ε3ε4, had both severe ARIA-E and ARIA-H; 20 days later, the participant died.
- The third participant, APOE genotype ε4ε4, had mild ARIA-H and had not recovered at the time of this report. The participant was also reported with mild ARIA-E and had recovered from the event.
- The remaining participant , APOE genotype ε4ε4, with severe ARIA-H was considered to be recovering at the time of this report. This participant also had severe ARIA-E and had recovered from the event.

Serious macro-haemorrhage event of haemorrhagic stroke was reported in 1 (0.1%) donanemab-treated participant:

- APOE genotype ε3ε4, in the donanemab group was a 70-80-year-old Caucasianwho was hospitalised with an SAE of haemorrhagic stroke, 1 month and 2 days after starting study treatment. The SAE was considered severe. In the opinion of the investigator, the SAE of haemorrhagic stroke was related to the study treatment, and the study treatment was permanently discontinued due to this SAE. The participant was reported to have recovered from the SAE.

During the AACI-PC period, 2 participants with an SAE of ARIA-H subsequently died. No donanemab-treated participants reportedly died due to macro-haemorrhage.

Treatment discontinuations due to ARIA-H and macro-haemorrhage

The incidence of ARIA-H events that led to treatment discontinuation were higher in donanemab-treated participants (n = 10, 1.2%) than placebo-treated participants (n = 3; 0.3%). Seven (0.8%) donanemab-treated participants discontinued treatment due to the TEAE of ARIA-H and 3 (0.4%) discontinued treatment due to the TEAE of superficial siderosis of the central nervous system.

One donanemab-treated participant discontinued treatment due to haemorrhagic stroke and another discontinued due to cerebral haemorrhage.

<u>All Dona</u>

ARIA-H (superficial siderosis and cerebral microhaemorrhage) was observed in 25.6% of participants treated with donanemab. Serious ARIA-H occurred in 0.3% of donanemab-treated participants. Most serious ARIA occurred early in the treatment period. A total of three donanemab-treated participants reported serious ARIA and subsequently died. Nearly all serious ARIA was symptomatic. Clinical symptoms associated with symptomatic and serious ARIA observed in All Dona were consistent with those reported in the placebo-controlled studies.

The frequency of macro-haemorrhages in All Dona was 1.3%. The applicant did not observe a pattern of haemorrhagic events beyond the known risk of microhaemorrhage was noted.

ARIA and macro-haemorrhage by subgroup analyses

APOE ε4 carrier status

Overall in the donanemab group, during the AACI-PC period,

- a higher incidence of ARIA-E was observed among APOE ε4 carriers (heterozygote carriers: n=103, 22.8%; and homozygote carriers: n=58, 40.6%) compared with non-carriers (n=40; 15.7%);
- similarly, a higher incidence of ARIA-H was observed among APOE ε4 carriers compared with non-carriers:
    - ARIA-H: APOE ε4 carriers (heterozygote carriers: n=146, 32.3%; and homozygote carriers: n=72, 50.3%) versus non-carriers (n=48, 18.8%).
    - ARIA-H micro-haemorrhage: APOE ε4 carriers (heterozygote carriers: n = 121, 26.8%; and homozygote carriers: n = 59, 41.3%) versus non-carriers (n = 39, 15.3%).
    - ARIA-H superficial siderosis: APOE ε4 carriers (heterozygote carriers: n=75, 16.6%; and homozygote carriers: n=40, 28.0%) versus noncarriers (n=19, 7.5%).
- Macro-haemorrhage was observed in 3 (0.7%) heterozygote APOE ε4 carriers and none in homozygote carriers or non-carriers.

In general, the homozygote APOE ε4 carriers are at a higher risk of developing ARIA than the heterozygote APOE ε4 carriers.

There were no clinically meaningful interactions of non-ARIA-related TEAEs by APOE ε4 carrier status and treatment group on the frequency of common TEAEs.

Antithrombotic medication use

The observed frequency of ARIA-E, ARIA-H, and macro-haemorrhage in participants using antithrombotic medications (at any time or within 30 days prior to the event) and those not using antithrombotic medications was similar within the donanemab- and placebo-treated groups. The findings were similar for all antithrombotic medication classes (aspirin, non-aspirin antiplatelets, and anticoagulants) within both treatment groups.

Baseline MRI findings

The baseline MRI findings were categorised as participants without micro-haemorrhage or superficial siderosis compared with those with either one or both of these findings. Overall, donanemab-treated participants with the above baseline MRI findings had a higher frequency of ARIA-E or -H post baseline. A similar pattern was observed in the placebo-treated participants. Due to the lower incidence of macro-haemorrhage events during the AACI-PC period, the applicant did not draw a conclusion on the effect of baseline MRI findings.

In addition to ARIA-E and ARIA-H, few participants were detected with new or worsened MRI findings of increase in white matter disease (placebo group: n = 8, 0.9%; donanemab group: n = 7, 0.8%) and other clinically meaningful abnormality type (placebo group: n =19, 2.2%; donanemab group: n = 25, 3.0%) during the AACI-PC period.

Tau levels

Baseline tau level was not associated with an increased ARIA risk.

ARIA incidence in restricted population of APOE4 non-carriers

Considering the high incidence of ARIA (and associated serious and fatal events) in the initial target population, safety was also assessed in restricted subpopulations with a lower risk of ARIA, based on APOE4 carrier status (exclusion of APOE4 homozygotes only; and exclusion of all APOE4 carriers).

In the table below, the most important ARIA events are summarised for the overall population versus the most recently proposed restricted target population of APOE4 non-carriers:

Table 28. ARIA events in overall and restricted target population of APOE4 non-carriers

Event	**Overall population**		**Restricted target population of APOE4 non-carriers**	
	Donanemab (N=853)(%)	Placebo (N=874)(%)	Donanemab (N=255)(%)	Placebo (N=250)(%)
ARIA/ICH-related death	0.35 (n=3)	0	0.39 (n=1)	0
ARIA (any)	36.8	14.9	24.7	12.0
Serious ARIA (any)	1.6	0	0.8	0
ARIA-E	24.0	2.1	15.7	0.8
Serious ARIA-E	1.5	0	0.4	0
Symptomatic ARIA-E	6.1	0.1	3.9	0
ARIA-H	31.4	13.6	18.8	11.2
Serious ARIA-H	0.5	0	0.4	0
Symptomatic ARIA-H	1.0	0.5	0.4	0.4
Macro-haemorrhage (intracerebral /intercranial)	1.3	0.8	2.0	0.4
Serious macro-haemorrhage	n.r.	n.r.	1.6	n.r.

Table made by the assessor. Based on Table 9.229 of responses to D180 LoQ and Table 2.2 of responses to D233 B/R MO. N.r. = not reported.

In the restricted target population, ARIA incidence (including serious and symptomatic ARIA) is lower than in the overall population. Overall, ARIA occurred in a quarter of patients (24.7%; ARIA-E: 15.7%, ARIA-H: 18.8%), and symptomatic ARIA in 4.3% of patients (3.9% ARIA-E, 0.4% ARIA-H). Serious ARIA occurred in 0.8% of patients. The incidence of macro-haemorrhagic events in the restricted population is still higher under donanemab, with serious macro-haemorrhages in 1.6% of patients, and mainly concerning subdural and subarachnoid haemorrhages.

One treatment-related death (due to ARIA-H and haemorrhagic stroke) occurred in an APOE4 non-carrier patient with baseline SS and a history of hypertension. After the second dose of donanemab, symptomatic ARIA-E occurred and treatment was withdrawn. While off treatment, the patient developed severe ARIA-H and cerebral haemorrhages and subsequently died.

Severe ARIA-E decreased from 1.6% to 0.4%, and severe ARIA-H from 10.4% to 4.3% compared to the overall population. Compared to overall, patients with ARIA in the restricted population also had proportionally less severe ARIA-E (2.5% vs. 6.9% overall) and less severe ARIA-H (22.9% vs. 33.3% overall). However, when ARIA-H superficial siderosis occurred in the restricted population (7.5% vs. 15.7% overall), it was more often severe than in the overall population (52.6% vs. 40.3% overall).

As in the overall population, the majority of first ARIA-E (>90%) and ARIA-H (>70%) occurred within 24 weeks of treatment initiation (by 6th infusion), and serious ARIA occurred within 12 weeks of

treatment initiation. ARIA recurrence rates in the restricted population are also largely comparable with the overall population and occur in a quarter of patients (both ARIA-E and -H).

Late during the procedure, the applicant provided additional data on APOE4 non-carriers in the All Dona safety set; the safety profile of non-carriers in All Dona is largely comparable to that of non-carriers in AACI-PC.

Study AACQ: ARIA incidence with enhanced dose titration

In Study AACQ (TRAILBLAZER-ALZ6), the effect of different dosing regimens (see Table 29 below) on ARIA-E incidence in adults with early symptomatic AD is compared to the standard dosing regimen of pivotal study AACI. Primary endpoint is ARIA-E incidence at Week 24, for which data collection is completed. Secondary endpoints include PK, PD (amyloid deposition), and ARIA-E/H incidences up to Week 76 (Study ongoing).

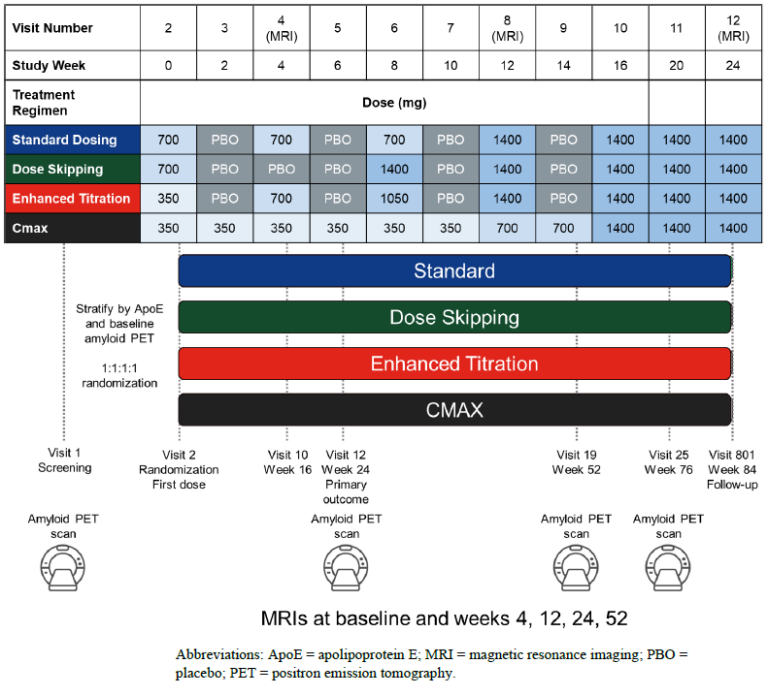
Table 29. Study intervention administered

		Donanemab
Dose	Standard	700 mg Q4W × 3 doses, then 1400 mg Q4W (for a total duration of up to 72 weeks)
	Dose Skipping	700 mg Q8W × 1 dose, then 1400 mg Q4W (for a total duration of up to 72 weeks)
	Enhanced Titration	350 mg Q4W × 1 dose, then 700 mg Q4W × 1 dose, then 1050 mg Q4W × 1 dose, then 1400 mg Q4W (for a total duration of up to 72 weeks)
	C_{max}	350 mg Q2W × 6 doses, then 700 mg Q2W × 2 doses, then 1400 mg Q4W (for a total duration of up to 72 weeks)
Route of administration		IV

Abbreviations: IV = intravenous; Q2W = every 2 weeks; Q4W = every 4 weeks; Q8W = every 8 weeks.

The design of Study AACQ is presented below:

Figure 14. Study design for study AACQ



Abbreviations: ApoE = apolipoprotein E; MRI = magnetic resonance imaging; PBO = placebo; PET = positron emission tomography.

The applicant considers that the 'enhanced titration schedule' could mitigate ARIA, and therefore these data are presented in the current report (note that this dosing regimen is not proposed at the time of this Opinion).

In the overall population, ARIA-E incidence at Week 24 with the 'enhanced titration schedule' was lower compared to standard titration (13.7% vs. 23.7%, respectively). ARIA incidence at Week 52 for the enhanced titration schedule versus standard titration is presented below, for the overall and restricted populations.

Table 30. ARIA incidence with standard vs. enhanced titration, in overall and restricted target population of APOE4 non-carriers

	Overall population		**Restricted population of APOE4 non-carriers**	
ARIA incidence	Standard titration (N=207) n (%) (52 Weeks)	Enhanced dose titration (N=212) n (%) (52 Weeks)	Standard titration (N=70) n (%) (52 Weeks)	Enhanced dose titration (N=73) n (%) (52 Weeks)
Treatment-related deaths	0	0.5 (n=1)	0	0
ARIA-E	24.2	15.6	15.7	13.5
Serious ARIA-E	0	0.5	0	1.4
Symptomatic ARIA-E	4.8	2.8	0	2.7
ARIA-H	27.5	25.0	17.1	18.9
Serious ARIA-H	0	0	0	0
Symptomatic ARIA-H	0	0.5	0	0
Macro-haemorrhage (based on TEAE cluster)	0.5	0.9	0	1.4

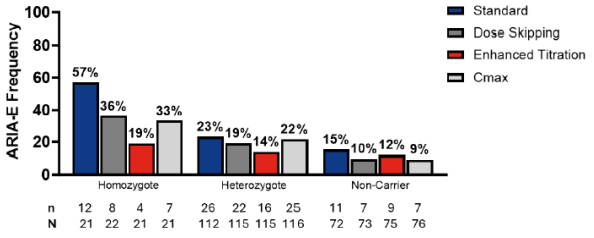
Based on Table 2.6 of the D195 responses to LoQ.

In the overall population, ARIA (-E/-H) incidence and severity at Week 52, including symptomatic ARIA-E, is lower with the enhanced titration schedule. Other safety events (deaths, SAEs, TEAEs, ARIA-H, hypersensitivity/IRRs, other AEs) seem largely comparable to the standard dosing group. The enhanced titration group demonstrated comparable brain amyloid plaque reduction (PD) up to Week 52 with the standard dosing group. In the restricted population, ARIA incidence and severity is largely comparable between the standard and enhanced titration regimens. Few cases of serious or symptomatic ARIA-E occurred, and only with enhanced titration.

Enhanced titration: ARIA incidence by APOE4 carrier status

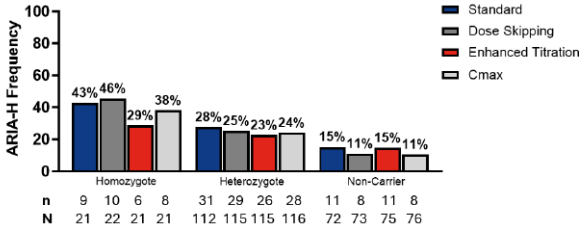
The incidence of ARIA-E (Figure 15) and ARIA-H (Figure 16) per dosing regimen (in colour) is presented by APOE4 carrier status (homozygotes, heterozygotes, non-carriers) below (from the 15T-MC-AACQ CSR):

Figure 15. ARIA-E frequency by APOE c4 status



Abbreviations: APOE ε4 = apolipoprotein subtype E allele 4; ARIA-E = amyloid-related imaging abnormalities–edema/effusions (also known as vasogenic edema); n = number of participants within each specific category; N = number of participants in the analysis population.
Source: Table AACQ.8.46

Figure 16. ARIA-H frequency by APOE C4 status



Abbreviations: APOE ε4 = apolipoprotein subtype E allele 4; ARIA-H = amyloid-related imaging abnormalities–hemorrhage/hemosiderin deposition; n = number of participants within each specific category; N = number of participants in the analysis population.
Source: Table AACQ.8.46

The effects on ARIA reduction with the enhanced titration schedule (red) compared to standard dosing (blue) are specifically observed in the APOE4 homozygote population, which are not part of the indicated population.

Hypersensitivity, anaphylaxis, and infusion-related reactions

Immediate hypersensitivity events

AACI-PC

More donanemab-treated participants (n=89; 10.4%) reported an immediate hypersensitivity event (i.e., on the same day of infusion) compared with the placebo- treated participants (n=8; 0.9%) (refer to Table 31). The most commonly reported events in the donanemab group were infusion-related reaction (IRR) (n=72, 8.7%), hypersensitivity (n=10, 1.2%), anaphylactic reaction (n=3, 0.4%), and urticaria (n=2, 0.2%).

Table 31. Summary of potential immediate hypersensitivity, anaphylactic, and infusion-related reactions occurring on the day of infusion, AACI

Event Category or Term	Placebo (N=874) n (%)		LY3002813 (N=853) n (%)	
Narrow Search on day of Infusion	8	(0.9)	89	(10.4)
Anaphylactic reaction (Algorithm) [*u]	0	(0.0)	3	(0.4)
Anaphylactic reaction (Narrow)	0	(0.0)	3	(0.4)
Hypersensitivity (Narrow)	8	(0.9)	89	(10.4)
Angioedema (Narrow)	0	(0.0)	3	(0.4)
Broad Search on day of Infusion				
Anaphylactic reaction SMQ (All Narrow and Broad terms)	9	(1.0)	14	(1.6)
Hypersensitivity SMQ (All Narrow and Broad terms)	11	(1.3)	96	(11.3)
Angioedema (All Narrow and Broad Terms)	5	(0.6)	17	(2.0)
Specified SMQ Narrow and Algorithm Terms [*v]				
Anaphylactic reaction (Narrow)				
Anaphylactic reaction	0	(0.0)	3	(0.4)
Hypersensitivity (Narrow)				
Infusion related reaction	3	(0.3)	72	(8.4)
Hypersensitivity	0	(0.0)	10	(1.2)
Anaphylactic reaction	0	(0.0)	3	(0.4)
Urticaria	0	(0.0)	2	(0.2)
Face oedema	0	(0.0)	1	(0.1)
Infusion related hypersensitivity reaction	0	(0.0)	1	(0.1)
Infusion site hypersensitivity	0	(0.0)	1	(0.1)
Rash	0	(0.0)	1	(0.1)
Dermatitis bullous	1	(0.1)	0	(0.0)
Dermatitis contact	3	(0.3)	0	(0.0)
Rhinitis allergic	1	(0.1)	0	(0.0)
Angioedema (Narrow)				
Urticaria	0	(0.0)	2	(0.2)
Face oedema	0	(0.0)	1	(0.1)

Source: Table AACI.8.200, CSR AACI. Abbreviations: N = number of subjects in the analysis population ; n = number of subjects with events meeting specified criteria; SMQ = standardised MedDRA query.

Symptoms

The most commonly reported symptoms by >15 donanemab-treated participants in the follow-up forms were: erythema (n = 42, 48.3%), chills (n = 35, 40.2%), nausea/vomiting (n = 33, 37.9%), sweating (n = 20, 23.0%), difficulty breathing/dyspnoea (n = 19, 21.8%), elevated blood pressure (n = 17, 19.5%), and other symptoms (n = 17, 19.5%).

Timing

Of the 87 donanemab-treated patients, 72 (82.8%) participants had events that occurred during treatment administration, and 16 (18.4%) participants had events within 30 minutes of end of treatment administration. Fourteen patients had events thereafter (but up to 24 hours from end of treatment).

Most donanemab-treated patients (71.4%) had their first (serious) hypersensitivity event by the 4th infusion.

The mean duration of immediate hypersensitivity/IRR TEAEs was 0.7 days with the median of 0.5 days.

Severity and seriousness

In the donanemab treatment group, of the 74 participants with IRR, 42 (57%) reported with mild severity, 29 (39%) as moderate, and 3 (4%) as severe. Of the 3 participants with anaphylactic reaction, 1 (33%) reported with mild severity, 2 (67%) with moderate severity. Of the 2 participants with angioedema, 1 (50%) reported as moderate and 1 (50%) as severe. Of the 10 participants with hypersensitivity, 3 (30%) reported as mild, 5 (50%) as moderate, and 2 (20%) as severe.

Three (0.4%) donanemab-treated participants and 1 (0.1%) placebo-treated participant ≥ 1 serious hypersensitivity, anaphylactic, or IRR event. No events were fatal.

Treatment discontinuation

Treatment discontinuations reported by more than 1 participant in the donanemab group include IRR (3.6%), hypersensitivity (0.5%), and anaphylactic reaction (0.4%), with no discontinuations due to these events in the placebo group.

<u>All Dona</u>

Immediate hypersensitivity events occurred in 9.0% of patients, mostly due to IRRs (7.9%). Serious IRR or hypersensitivity was uncommonly reported (0.5%) and included 4 SAEs of anaphylaxis (0.1%).

In participants treated with donanemab who had an immediate hypersensitivity event, the severity of

IRR TEAEs were mild (56.5%), moderate (38.4%), and severe (5.1%);

Anaphylactic reaction TEAEs were mild (37.5%), moderate (50%), and severe (12.5%);

Hypersensitivity TEAEs were mild (33.3%), moderate (46.7%), and severe (20%).

In all donanemab-treated patients, 13 (0.5%) treatment-emergent SAEs were observed: 6 events of IRRs, 3 events of anaphylactic reaction, 1 event of anaphylactic shock, 1 event of drug eruption, 1 event of infusion-related hypersensitivity reaction, and 1 event of urticaria.

The majority (>59%) of first-onset IRRs occurred by the third infusion and the majority resolved within less than 24 hours (median 0.5 days, mean 0.9 days). All 14 serious IRR/Hypersensitivity events occurred by the fourth infusion.

Interventions

Although slowing of infusion and prophylactic medication were common interventions to reduce the risk of an IRR on rechallenge, the frequency of IRRs with and without these interventions was similar. In participants who received prophylaxis medication for rechallenge, 39.5% experienced an IRR, while in participants without prophylaxis, 42.1% experienced an IRR. At the rechallenge infusion, 41.7% of participants with slowed infusions experienced an IRR, compared with 41.3% without slowed infusions.

Non-immediate hypersensitivity events

AACI-PC

A similar proportion of donanemab-treated participants (n = 47; 5.5%) reported non-immediate events of hypersensitivity, anaphylactic reaction, or angioedema (i.e., on the day after the infusion or later), compared with placebo (n = 39; 4.5%). The most common event was rash (donanemab: n = 15 [1.8%]; placebo: 14 [1.6%]).

All Dona

Non-immediate hypersensitivity events were reported in 4.1% of participants treated with donanemab, with rash the most commonly reported event. All non-immediate hypersensitivity events were mild or moderate in severity.

- ***Laboratory findings***

In AACI-PC, no clinically meaningful differences were observed across treatment groups in potentially clinically significant laboratory abnormalities, including blood haematology, chemistry, and urinalysis.

- In haematology analytes, difference in shifts from normal/high to low and from normal/low to high were observed between placebo and donanemab groups at single time points for blood neutrophils high at Visit 8 (Week 24) and blood lymphocytes low at Visit 15 (Week 52).
- With regard to serum chemistry, more participants in the donanemab group (5.5%) compared with the placebo group (3.3%) had an increase from baseline in serum ALT at any time post baseline. Three participants in the donanemab group and 2 participants in the placebo group had at least one of the following: ALT ≥5x ULN, AST ≥5x ULN, ALP ≥3x ULN, ALT or AST ≥3x ULN, and bilirubin ≥2x ULN. Two of the donanemab-treated participants met criteria for hepatotoxicity. In addition, one participant in the donanemab group discontinued from the study due to the AE of Hepatic enzyme increased. The ALT and/or AST increases ≥3x ULN in 5 other donanemab-treated participants with maximal bilirubin levels <2x ULN were not accompanied by symptoms and were transient.
- With regard to urinalysis, no clinically significant differences were observed across treatment groups for TE abnormalities in parameters.

- ***In vitro biomarker test for patient selection for safety***

N/A

- ***Safety in special populations***

The clinical studies enrolled patients aged 60 to 85 years of age. Older patients reported numerically more adverse events, including serious events, compared to younger patients.

No difference in common AE profile between patients of different gender, race, ethnicity and geographic region was noted.

The observed safety profile of the high tau population was similar to the overall safety population.

APOE ε4 carrier status was significantly related to the frequency of ARIA-E and ARIA-H.

- ***Immunological events***

A total of 88.1 % donanemab-treated patients tested positive for treatment-emergent anti-drug antibodies (ADA) and all of the patients with ADA had neutralizing antibodies (NAb).

Although an effect of ADA titre on PK was identified by the applicant, no association was observed between presence or titre of ADA and clinical efficacy of donanemab. In contrast, IRRs occurred more frequently in participants in the upper ADA titre group. Of all donanemab-treated patients with IRR in the placebo-controlled studies (AACG, AACI), the distribution of patients reporting IRR was:

  - 32.9% in the upper titre group, constituting 56.1% of patients reporting IRR;
  - 7.1% in the middle titre group, constituting 30.5% of patients reporting IRR;
  - 2.3% in the lower titre group, constituting 13.4% of patients reporting IRR.

- ***Safety related to drug-drug interactions and other interactions***

DDIs are unlikely, as donanemab is an antibody that is not metabolised by hepatic cytochrome P450 enzymes.

Although the use of antithrombotic medications has been identified as an aggravating factor for ARIA-H with other monoclonal antibodies directed against Aβ, antithrombotics were not prohibited as concomitant treatment in the clinical studies on donanemab. Antithrombotic use was similar among participants in the donanemab and placebo group (~40% in both groups). The use of non-aspirin antiplatelets was higher in the donanemab group (6.1%) compared with the placebo group (3.8%). The most commonly used antithrombotic in both groups was aspirin.

- ***Discontinuation due to adverse events***

<u>AACI-PC</u>

The frequency of participants who discontinued study treatment due to AEs was higher in the donanemab group (13.1%) compared with the placebo group (4.3%) (refer to Table 32).

Most patients on donanemab stopped treatment due to IRR (3.6%) or ARIA (ARIA-E: 2.5%, ARIA-H: 0.8%; superficial siderosis of CNS: 0.4%).

Treatment withdrawal due to any event of IRR/hypersensitivity is around 4.7%, when taking into account other relevant PTs (i.e., hypersensitivity [0.5%], anaphylactic reaction [0.4%], cytokine release syndrome [0.1%], infusion related hypersensitivity reaction [0.1%]).

Table 32. Permanent discontinuation of study treatment due to adverse events [≥ 0.5%] by PT by decreasing frequency, AACI-PC

AEs Leading to Treatment Discontinuation	Placebo (N = 874) n (%)	Donanemab (N = 853) n (%)
Participants with treatment discontinuation due to AEs	38 (4.3)	112 (13.1)
IRR	0	31 (3.6)
ARIA-E	3 (0.3)	21 (2.5)
ARIA-H	2 (0.2)	7 (0.8)
Hypersensitivity	0	4 (0.5)

Abbreviations: AE = adverse event; ARIA-E = amyloid-related imaging abnormality–edema/effusions (also known as vasogenic edema); ARIA-H = amyloid-related imaging abnormality–microhemorrhages and hemosiderin deposits (including brain microhemorrhage and superficial siderosis); IRR = infusion-related reaction; PC = placebo-controlled.

Source: Table AACI.8.180

All Dona

The frequency and types of AEs leading to treatment discontinuation reported were similar to those observed in the placebo-controlled studies. A total of 265 (9.7%) participants discontinued treatment due to any AE. Discontinuations due to an AE were highest in the Nervous system disorder SOC, driven by ARIA-related events, and SOC Injury, poisoning, and procedural complications SOC, driven by IRR.

- ***Post marketing experience***

Donanemab has recently been approved in the US (July 2024), Japan and the UK, but no post-marketing data are available yet.

2.6.9. Discussion on clinical safety

The main body of evidence for the safety of donanemab originates from the randomised, double-blind, placebo-controlled single pivotal study AACI-PC. Safety data from the pivotal study were held against an integrated safety set with (additional) data from the placebo-controlled phase 2 study AACG, the double-blind extension study of AACI (AACI-LTE), and three open-label studies (AACI-safety addendum, AACH-B, and AACN).

Up till the initial data lock, 964 patients were exposed to donanemab at the recommended dose (i.e., 3 x 700 mg Q4W and 1400 mg Q4W thereafter) for at least 12 months, and 215 patients have exposure data up to 76 weeks (18 months). This is acceptable and in line with the ICH requirements. In the pivotal study AACI-PC, 510 patients were exposed to donanemab for at least 12 months, and 174 patients for at least 72 weeks. This did not necessarily concern, however, the recommended dose. For example, in case of ARIA, the lower titration dose (i.e., 700 mg) could be continued either temporarily or throughout the remainder of the treatment period. Furthermore, 43 patients started treatment with 1400 mg Q4W. In the pivotal study 83.6% of patients received donanemab at the recommended dose; while 11.1% had delayed titration (>3 doses of 700 mg), mostly due to ARIA prior to the 4th dose. Almost 40% of donanemab-treated patients had dose suspensions, with a median duration of 59 days (min. 28 days - max. 325 days), mostly due to ARIA. Changes in dosing did not appear to impact safety in patients with ARIA (refer to efficacy assessment).

Based on the initial proposed posology, around one fifth of patients would have needed to continue treatment after 18 months based on insufficient amyloid reduction, although safety data beyond 18 months of treatment are not available. A discussion on stopping criteria was requested. In response, the applicant amended the maximum treatment duration to 18 months.

Adverse events are dominated by ARIA-E (24.0%) and ARIA-H (31.4%). Based on radiographic results, almost half of the ARIA-E events (44%) were concurrent with ARIA-H. The incidence of hypersensitivity reactions (10.4%), mainly infusion-related reactions (IRR; 8.7%), was also high.

The adverse drug reactions (ADRs) initially identified by the applicant were ARIA-E, ARIA-H, headache, IRR, nausea, vomiting, and anaphylactic reaction. The ADR list was not acceptable, and several updates to the ADR table and description of selected adverse reactions were requested (e.g., concerning macro-haemorrhage, ARIA symptoms, and IRR/hypersensitivity events). These are now adequately implemented.

The difference in serious AEs between placebo and donanemab (15.8% vs. 17.4%, resp.) was mainly driven by serious events of ARIA-E and ARIA-H; these were not observed in the placebo group.

More patients died in the donanemab group than in the placebo group (1.9% vs. 1.1% , resp.), which is of concern. The applicant indicated that 3 deaths were due to donanemab-related ARIA-E and/or ARIA-H. Several fatal brain haemorrhagic events were, however, also associated with donanemab treatment. In All Dona, 6 deaths were at least possibly related to donanemab treatment. Five of these included events of ARIA-E and/or ARIA-H, 1 concerned a macro-haemorrhage without ARIA (thalamic haemorrhage), and in 2 patients ARIA was accompanied by or preceded macro-haemorrhage(s). In Study AACQ, a seventh death linked to donanemab treatment was reported. Six fatal cases all concerned APOE4 heterozygote patients, and one concerned an APOE4 non-carrier patient. In the post-marketing setting, one ARIA-associated death (unknown APOE4 carrier status) has been referred to so far.

ARIA was identified as an AE of special interest as it is known to occur with anti-amyloid monoclonal antibodies. The management plan of ARIA evolved during the donanemab clinical programme, based on observations during the studies. In principle, that meant moving to a more cautious approach. Analyses indicated that the initially applied dose titration step, unexpectedly, did not impact the frequency of ARIA, while serious ARIA occurred slightly less, and symptomatic ARIA occurred slightly more often with titration. The limited data do not allow firm conclusions on the effect of dose titration, but this step could be accepted considering that most patients in the pivotal trial were treated accordingly.

During the procedure, the applicant submitted preliminary results (up to Week 52) of the Phase 3b Study AACQ, in which the effect of different donanemab dosing titration regimens on ARIA-E (and amyloid lowering) was investigated in adults with early symptomatic AD. Based on these results, the applicant would like to discuss whether it is acceptable to implement a new ('enhanced') dosing titration schedule, which is different from the titration applied in the pivotal study (see also below).

ARIA-E

More than half of all initial ARIA-E events occurred after receiving 3 infusions, and most first ARIA-E episodes (n=182) occurred by the 6th infusion. Initial events still occurred around 1 year of treatment (scheduled MRI) though. ARIA-E events took a median ~two months to resolve radiographically. Approximately a quarter of patients had recurrent events, with up to four events of ARIA-E in six patients. In contrast, placebo-controlled patients never had a second event of ARIA-E. The majority of second ARIA-E event occurred after the 4th infusion; while third and fourth ARIA-E episodes mainly occurred at/after the 6th infusion. ARIA-E events seem to fully diminish over the course of the study (18 months).

A quarter of donanemab-treated patients with ARIA-E had symptoms (25.4%, i.e., 6.1% of all donanemab-treated patients). Mostly, they concerned headache and confusion, but also seizures were reported. In 85% of the patients with symptomatic ARIA-E (44/52), symptoms resolved. Most serious and/or symptomatic ARIA-E events were treated with supportive treatment, including steroids. Additional analyses indicated that the effects of corticosteroids or other supportive treatment on the duration or symptomatic and radiographic resolution of (first episodes of) ARIA-E could not be established. A proportion of donanemab-treated patients with symptomatic ARIA-E (15%) continued to have clinical symptoms, which is concerning. In contrast, there was only one placebo patient with symptoms and those resolved. The applicant clarified that of the 8 patients with unresolved symptoms, 3 patients had in fact died. Unresolved ARIA-E symptoms in the other 5 were: aphasia; seizure; dementia; somnolence and confusional state; and balance disorder and diplopia (latter resolved after data lock). Three patients with serious events (seizure, aphasia, dementia) received supportive treatment. Radiographic resolution of ARIA-E was reported in all except one patient (resolution not documented for seizure) prior to their study withdrawal due to unresolved symptoms. This implies there can be long-term sequelae of ARIA-E, also after its radiographic resolution, though they may perhaps be rare.

ARIA-related symptoms could be masked by symptoms of AD, e.g., confusion or effects on cognition. The applicant was requested to provide an overview/comparison of AEs reported in patients within 4 weeks prior to an ARIA event and after the ARIA. Apart from a temporal relationship between ARIA-H and ARIA-E events, no other notable differences in AE reporting were identified. The applicant presented analyses on iADRS13, MMSE, and ADAS-Cog changes in patients with and without ARIA-E, and these do not indicate a different response over time (up to Week 76).

ARIA-H

Around a third of patients (31.2%) treated with donanemab experienced an event of ARIA-H (25.0% microhaemorrhages; 16.0% superficial siderosis) versus 13.6% in the placebo group. Most initial ARIA-H events occurred within the first 6 months of treatment, but initial events are noted up to 18 months of treatment. This could reflect natural occurrence of ARIA-H. Based on the integrated placebo-controlled data set (AACG + AACI), around 2/3 of patients with ARIA-H experienced one ARIA-H event, while a third of patients experienced two to six events. New episodes were generally more severe. Second episodes occurred throughout the treatment period. Most 3rd , 4th , 5th and 6th recurrences were observed relatively early in treatment; the majority between infusion 2 and 7, although they were noted also late in treatment. Thus, ARIA-H events occur throughout study duration, although less frequently later on, and have not weaned at 18 months.

Apart from MRI findings, 'Macro-haemorrhage' was evaluated by the PTs Cerebral haemorrhage and haemorrhagic stroke. The applicant was requested to present an overview of all cases of cerebral and intracranial haemorrhages under donanemab, i.e., including but not limited to cerebral haematoma, thalamic haemorrhage, subarachnoid haemorrhage, subdural haemorrhage and subdural haematoma. Based on TEAE or MRI findings meeting these extended search criteria, macro-haemorrhagic events occurred more often in donanemab-treated patients than in placebo patients (1.3% vs. 0.8%, resp.; All Dona: 1.3%). More than half of cases had concurrent ARIA-H and/or ARIA-E (All Dona). Considering the higher incidence of brain haemorrhages under donanemab, the causal relationship with donanemab in several patients, the mechanism of action and known class effect, 'macro-haemorrhage' is considered an ADR of donanemab. The SmPC has been updated to include 'intracranial haemorrhage', to reflect brain haemorrhages also beyond cerebral haemorrhages.

Although antithrombotic use was reported not to impact the frequency of ARIA-H events, concomitant antithrombotics (including anticoagulants) could potentially be associated with more severe or serious ARIA-H, or macro haemorrhagic (cerebral or intracranial) events. Analysis per type of antithrombotic

medication (aspirin, non-aspirin antiplatelets, and anticoagulants) on ARIA-H and macro-haemorrhage severity did not reveal a clear pattern different than that observed for antithrombotics overall, although numbers were small. Concomitant use with thrombolytics was rare, but in two of the four patients it led to fatal haemorrhages, and a role of donanemab in aggravation of events was considered possible. Since thrombolytic therapy should not be avoided in case it is required, additional warnings related to thrombolytic therapy are endorsed (i.e., to assure a diagnosis of ischemic stroke and rule out ARIA-E, and to consider alternative treatment approaches [such as thrombectomy] in case ischemic stroke occurs in the presence of ARIA-E). The high mortality with concomitant thrombolytic therapy remains a large concern. The SmPC recommendations in case of concurrent use with antithrombotic medication (anticoagulants and thrombolytic therapy) are acceptable.

ARIA mitigation

Dosing recommendations

It was initially not clear which actions were taken with donanemab in response to ARIA-E or ARIA-H in study AACI-PC. Based on the integrated placebo-controlled data set (AACG + AACI), actions seemed to differ per ARIA-E severity and episode number. Importantly, it was not clear how effective they were, and how they related to the proposed ARIA management recommendations in the SmPC. The applicant clarified that in the pivotal study, dosing actions taken in response to ARIA did not always follow the study protocol, which is more or less (but not fully) in line with the proposed SmPC (i.e., continue or temporarily suspend dosing, depending on ARIA severity and symptomatology). This was specifically the case for moderate to severe ARIA(-E/-H) and symptomatic ARIA-E. Based on the presentation of (aggregated and patchy) data, assessment of the most appropriate dosing advice in case of ARIA is not straightforward. Data do not necessarily indicate that the proposed recommendations lead to better resolution and recurrence rates than alternative dosing options. However, considering that the majority of patients were treated according to the study protocol's instructions, which are largely in line with the dose recommendations in the proposed SmPC, the recommendations can be accepted. Serious ARIA is now included as permanent stopping criterium, in line with the study protocol and actions taken.

Patients who developed >4 microhaemorrhages and >1 area of superficial siderosis during the course of the study had an increased risk of subsequent severe ARIA events. The applicant was asked to discuss permanent stopping rules related to these MRI findings, to mitigate the risk of severe ARIA events. This would complement the applicant's SmPC text proposal to re-assess risk factors prior to re-starting treatment with donanemab after an ARIA event. The applicant eventually implemented permanent stopping rules in case of serious and multiple severe ARIA events, and the amended SmPC text proposal for dosing or treatment discontinuation is now considered acceptable.

MRI monitoring

Initially, the recommended monitoring for ARIA in the SmPC was: MRI within one year prior to initiating treatment, and prior to the second dose, prior to dose increase, and prior to the seventh dose. First, a more recent MRI prior to treatment starts was deemed necessary, considering the changes in MRI findings over one year in at least 10% of patients. The applicant agreed to include a more recent baseline MRI (within 6 months). Second, although most first (serious) ARIA events were observed within six months weeks after starting treatment, more frequent monitoring (before and after the seventh dose) may have been warranted, to aid in earliest detection of all ARIA, including recurrent events. For example, a peak of ARIA events occurs prior to 3rd infusion. Based on these data, the applicant included an additional MRI prior to 3rd dose for all patients, which was agreed. The added value of the intensified MRI monitoring for the restricted population of non-carriers is less clear, and therefore, the MRI monitoring schedule used in the pivotal trial is deemed acceptable (i.e., without an extra MRI prior to third dosing). Further, mandatory MRI after the seventh dose was not considered warranted, due to lower ARIA risk beyond 6 months of treatment. The proposed SmPC provides

prescribers the freedom to require additional MRIs at any time, if deemed indicated based on symptom occurrence, which can be supported.

Finally, the effectiveness and feasibility of MRI monitoring in clinical practice is not yet sufficiently addressed and would need to be followed up in post-authorisation studies.

Restricted target population

APOE ε4 carrier status and specific baseline MRI findings (presence of microhaemorrhage, superficial siderosis) were the factors most strongly associated with increased frequency of ARIA events in the clinical studies. ARIA frequency more or less halved per APOE ε4 allele less. Similarly, the frequency of severe, serious and symptomatic ARIA events was highest in homozygote carriers. The association with APOE ε4 carrier status was not apparent for macro haemorrhagic and fatal events, which were most often observed in heterozygote carriers and non-carriers, although data are limited. A discussion was requested on whether patients with strong risk factors for ARIA, i.e., APOE ε4 carrier status and/or baseline MRI findings (presence of microhaemorrhage, superficial siderosis), should be subjected to an intensified ARIA monitoring and management plan. For specific baseline MRI findings, contraindications are now proposed (see later). Further, the applicant initially proposed to exclude the patients at highest risk of ARIA, i.e., APOE4 homozygote carriers, from treatment with donanemab. However, the remaining population of APOE4 heterozygote carriers and non-carriers was still at high risk of ARIA and, importantly, ARIA-associated fatal events were not significantly reduced. The applicant proposes to restrict the target population to APOE4 non-carriers only. All APOE4 carriers will thus be excluded from treatment with donanemab. The remaining target population is 29% of the study population. Due to the restriction of the target population, APOE4 testing will become obligatory prior to treatment with donanemab, and information on APOE testing is now reflected adequately throughout the SmPC.

Within the restricted target population, ARIA incidence is reduced by ~12% compared to the overall population, but is in absolute term still very high, occurring in a quarter of patients (any ARIA: 24.7% vs. 36.8, resp.; ARIA-E: 15.7% vs. 24.0%, resp.; ARIA-H: 18.8% vs. 31.4%, resp.) . Serious and symptomatic ARIA was lower in the restricted population compared to overall (serious ARIA: 0.8% vs. 1.6%, resp.; symptomatic ARIA-E: 3.9% vs. 6.1%, resp.). The incidence of macro haemorrhagic events in the restricted population was still higher under donanemab, and mainly concerned subdural and subarachnoid haemorrhages (2.0% vs. 0.4% with placebo). Serious macro-haemorrhagic events occurred in 1.6% of patients in the restricted population. One fatal case occurred in an APOE4 non-carrier. This patient, with a history of hypertension, also had baseline SS. Baseline SS is currently a contraindication for use. The safety profile of non-carriers in the 'All Dona' integrated safety set was largely comparable to that of non-carriers in the pivotal trial.

'Enhanced titration' schedule

To further minimise the risk of ARIA, the applicant has been investigating a new 'enhanced titration' schedule, which is currently investigated in study AACQ. Interim results from Study AACQ indicate that overall, ARIA (-E/-H) incidence at Week 24 and Week 52, including symptomatic ARIA-E, is lower with the enhanced titration schedule compared to standard dosing, while PK and amyloid reduction is comparable. However, the effect on ARIA incidence is mainly driven by APOE4 homozygote patients. Indeed, in the restricted population of APOE4 non-carriers, ARIA incidence is comparable between the two dosing regimens, and the few serious/symptomatic ARIA events that occurred, were observed with the enhanced titration. Thus, the safety benefit of enhanced titration in the restricted target population is not apparent. The ARIA profile in the titration study (e.g., number and timing of serious ARIA), does not match the ARIA profile observed in pivotal study AACI-PC, and it is thus difficult to ascertain what will eventually be the ARIA picture in clinical practice. Importantly, it is also not clear to what extent the new dosing schedule in Study AACQ leads to similar efficacy findings as in the pivotal study since no efficacy outcomes are included, and there is no established relationship between the reduction of

cerebral amyloid beta and efficacy outcomes. As such, comprehensive data on the safety and efficacy in the proposed restricted target population, with the enhanced titration schedule, are not currently available.

Other risk minimisation measures

Initially, no contra-indications were proposed by the applicant, although there were several exclusion criteria in the pivotal study based on grounds of safety (i.e., pre-existing ARIA-E, >4 microhaemorrhages, >1 area of superficial siderosis, any macro-haemorrhage, or severe white matter disease). Factors that can also be indicative of cerebral amyloid angiopathy. One of the seven fatal cases related to donanemab occurred in a patient (APOE4 non-carrier) with baseline SS. Furthermore, patients who developed macro-haemorrhage or 'severe white matter disease' during the course of the studies were never re-dosed. The SmPC also states that in case of macro haemorrhage, treatment should be permanently discontinued. Based on these safety grounds, the applicant agreed to update the list of contra-indications to include: 'Baseline MRI findings of prior intracerebral haemorrhage greater than 1 cm, >4 microhaemorrhages, superficial siderosis, or vasogenic oedema (ARIA-E), or other findings, which are suggestive of cerebral amyloid angiopathy (CAA)' and 'severe white matter disease'.

The risk of ARIA is related to donanemab exposure (Cav, ss) and influenced by weight. Low-body weight patients are expected to have higher overall exposure (popPK modelling) with the proposed flat dose for donanemab. The applicant quantified the increased risk of ARIA in low body weight patients with the proposed flat dose regimen, and as it is lower than that of other identified risk factors (e.g. APOE ε4 status), no minimisation measures are deemed necessary.

Brain volume loss and long-term safety

Recently, anti-ß amyloid therapies were linked to accelerated brain volume loss (Alves et al., 2023[1]). In both AACG and AACI, donanemab-treated participants had significantly greater reduction in whole brain volume than placebo-treated participants. Donanemab generally causes a reduction in plaque load by 24 weeks, but whole brain volume loss separates from placebo after 24 weeks, with volume loss increasing up to 76 weeks (Mintun et al., 2021[2]). This suggests that these changes may not solely be explained by plaque removal. The applicant was requested to elaborate on alternative explanations, e.g., to what extent the brain volume changes could be related to prior or recurrent ARIA events, or other non-ARIA causes. The applicant reflected on mechanisms (e.g. amyloid dynamics, such as alterations in morphology and/or neuroinflammatory response, or fluid shifts between intra- and extracellular or intravascular compartments) and measurements that could provide insight into this phenomenon. Such measurements, for example of brain microstructural changes (e.g., with diffusion tensor imaging) were not acquired in AACG or AACI though and mechanisms remain hypothetical. Brain volume changes over time were requested for study AACI; as well as analyses on brain volume changes and cognitive changes, without and after ARIA stratification. Patients with ARIA-E or ARIA-H showed a similar decrease in whole brain volume as those without ARIA-E or ARIA-H. In contrast, patients with ARIA-E had a numerically larger increase in bilateral ventricles than those without ARIA-E (in line with the literature); and the smallest numerical decrease in hippocampal volume. No difference on clinical outcomes (iADRS, CDR-SB) was reported in patients with versus without ARIA-E. The clinical relevance of brain volume changes, and possible impact of ARIA, in the current therapeutic context and with the measurements available, remains uncertain. In that regard, it is relatively reassuring that

[1] Alves F, Kalinowski P, Ayton S. Accelerated Brain Volume Loss Caused by Anti-β-Amyloid Drugs: A Systematic Review and Meta-analysis. Neurology. 2023 May 16;100(20):e2114-e2124. doi: 10.1212/WNL.0000000000207156. Epub 2023 Mar 27. PMID: 36973044; PMCID: PMC10186239.
[2] Mintun MA, Lo AC, Duggan Evans C, Wessels AM, Ardayfio PA, Andersen SW, Shcherbinin S, Sparks J, Sims JR, Brys M, Apostolova LG, Salloway SP, Skovronsky DM. Donanemab in Early Alzheimer's Disease. N Engl J Med. 2021 May 6;384(18):1691-1704. doi: 10.1056/NEJMoa2100708. Epub 2021 Mar 13. PMID: 33720637.

treatment duration will not extend beyond 18 months. Safety results from the LTE study available so far are also reassuring in that respect. Overall post-treatment safety appears similar in those with and without a prior ARIA event during the treatment period, with one exception; a higher frequency of ARIA-E/H events observed in the group with a previous ARIA event compared with the placebo-group from the initial AACI placebo-controlled period. The increased frequency of ARIA events post-treatment was primarily driven by ARIA-H events.

Hypersensitivity/IRR

Immediate hypersensitivity reactions were also deemed AESI. They occurred more often in donanemab-treated patients compared to controls (10.4% vs. 0.9%, resp.). Most often, they concerned IRR (8.7%). The majority of the first-onset IRRs occurred by the fourth infusion and most events resolved the same day. It is noted that some immediate events of hypersensitivity lasted up to 64 days, with a maximum duration of serious immediate hypersensitivity events of 4.5 days. The applicant clarified that most IRR/hypersensitivity cases of longer duration were non-immediate events (e.g., contact dermatitis, rash erythematosus, rash, or urticaria), that were not considered related to donanemab and resolved without supportive treatment. The 17 (13.4%) donanemab-related IRR/hypersensitivity events of longer duration (>2 days, up to 111 days) concerned IRR (e.g., headache, fatigue, nausea/vomiting), hypersensitivity, drug eruption, and urticaria. Event duration was in some cases relatively long (e.g. 30 days for IRR headache) but usually resolved without supportive care (except in n=3). Two related events of longer duration were serious (IRR with collapse [4 days], Drug eruption with erythematous rash [20 days]) and led to treatment/study withdrawal.

In the pivotal study, all (3/3) patients with an anaphylactic reaction, 31/72 (43%) of patients with an IRR, and 4/10 (40%) patients with a hypersensitivity event permanently discontinued treatment with donanemab. Of all patients with an initial IRR/hypersensitivity event (All Dona), 65% was rechallenged. Rechallenges occurred mostly after mild events (74.4%). Rechallenge led to subsequent IRR/hypersensitivity events in 63.4% of patients, with severity and type of symptoms usually similar to that of initial events. Increase in severity of symptoms occurred in 8.2% of patients with an initial mild event. Taking into account all IRR/hypersensitivity events (i.e., initial and upon rechallenge), 129 of 252 patients with an IRR/hypersensitivity event (51%) withdrew treatment due to the event, in line with results of the pivotal. It confirms the high treatment drop-out due to IRR/hypersensitivity events. The SmPC has been updated to reflect the outcome of hypersensitivity events after rechallenge. For patients with an IRR who did re-start treatment, prophylactic medication or slowed infusion did not prevent a subsequent IRR upon rechallenge infusion (All Dona). Thus, these events cannot be mitigated.

In the restricted population of APOE4 non-carriers, hypersensitivity events occurred in 7.8% of patients, which is in line with the overall population.

The incidence of anti-donanemab antibodies (ADA) is very high (88.1%), with neutralizing antibodies present in all of the patients with ADA. Although ADA titre was not related to the risk of ARIA, it was associated with the incidence of IRR/immediate hypersensitivity events. This is now captured adequately in the SmPC.

2.6.10. Conclusions on the clinical safety

The safety profile of donanemab largely reflects previous observations on anti-Aß monoclonal antibody treatment, i.e., it is dominated by ARIA-E and ARIA-H events. Hypersensitivity reactions, mainly injection-related reactions, also occur commonly. Although the majority of ARIA events appear mild to moderate in MRI severity and asymptomatic, part of the patients do experience severe and/or symptomatic events (e.g., seizure, aphasia). In a restricted population of APOE4 non-carriers, safety

improves compared to the overall population. Though, ARIA incidence remains substantial; ARIA occurs in a quarter of donanemab-treated patients, twice as much as under placebo. Although less common compared to the overall population, symptomatic ARIA (4.3%) and serious ARIA (0.8%) also occurred in the restricted population. One ARIA-related fatal event occurred in an APOE4 non-carrier. Concerns remain that treatment-related deaths may not be prevented in this subgroup of patients either, for example in case of (e.g., cardiovascular) co-morbidities, or when antithrombotic medication is used (e.g., thrombolytic therapy), or in case risk minimisation measures are not strictly applied by the treating physicians. Although long-term consequences of ARIA and the observed decreases in brain volume after donanemab treatment are uncertain, treatment duration is limited (18 months) and immediate post-treatment effects on cognition not apparent. Thus, the safety profile of donanemab improves with the newly proposed measures and restrictions, but the high incidence of ARIA and risk of fatalities remain a concern. Concerns also remain on the effectiveness and feasibility of the risk minimisation measures in clinical practice. Thus, the safety of donanemab is not sufficiently substantiated.

2.7. Risk Management Plan

2.7.1. Safety concerns

Table 33. Summary of safety concerns (RMP table SVIII.1)

Summary of safety concerns	
Important identified risks	ARIA-E (cerebral oedema/effusion) ARIA-H (cerebral microhaemorrhage and superficial siderosis) Hypersensitivity events (including IRR)
Important potential risks	Intracranial haemorrhage
Missing information	None

2.7.2. Pharmacovigilance plan

Table 34. Ongoing and planned additional pharmacovigilance activities

Study **Status**	**Summary of Objectives**	**Safety Concerns Addressed**	**Milestones**	**Due Dates**
Category 1 – Imposed mandatory additional pharmacovigilance activities that are conditions of the marketing authorisation				
Secondary database study to characterise safety, drug utilisation, and effectiveness of additional risk minimisation activities in	The objectives of this observational study, which will be conducted in donanemab-treated patients in routine clinical practice in the EU, are to describe • the incidence of serious hypersensitivity reactions and intracranial haemorrhage[a]	• Hypersensitivity events (including IRR) • Intracranial haemorrhage	Protocol submission Study progress reports	Within 6 months of EU regulatory approval To be provided with the PSUR/PBRER

Study Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
donanemab-treated patients in the EU. Planned	• drug utilisation (including, use by patients with Down syndrome and users of antithrombotic or thrombolytic medications), and • the effectiveness of additional risk minimisation activities.		Final study report submission	31 December 2030
Registry-based observational study to characterise ARIA within a cohort of donanemab-treated patients in the EU Planned	The objectives of this study are to describe • the incidence of symptomatic ARIA (ARIA-E and ARIA-H), asymptomatic ARIA, hypersensitivity events, and intracranial haemorrhage[a] within a cohort of donanemab-treated patients in routine clinical practice in the EU, and • intracranial haemorrhage within the subgroup of patients using concomitant anti-thrombotic or thrombolytic medications.	• ARIA-E (cerebral oedema/effusion) • ARIA-H (cerebral microhaemorrhage and superficial siderosis) • Hypersensitivity events (including IRR) • Intracranial haemorrhage	Protocol submission Study progress reports Final study report submission	Within 6 months of EU regulatory approval To be provided with the PSUR/PBRER 31 December 2031
Category 2 – Imposed mandatory additional pharmacovigilance activities that are specific obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
None				
Category 3 – Required additional pharmacovigilance activities				
Healthcare provider survey to assess the effectiveness of the donanemab additional risk minimisation activities in the EU Planned	The objectives of the survey are to assess • prescriber and radiologist understanding of the important safety risks related to the use of donanemab detailed in the HCP educational materials, that is, information relating to ARIA-E (cerebral oedema/effusion), ARIA-H (cerebral microhaemorrhage and	• ARIA-E (cerebral oedema/effusion) • ARIA-H (cerebral microhaemorrhage and superficial siderosis) • Intracranial haemorrhage	Protocol Submission Final study report submission	Within 6 months of EU regulatory approval Anticipated 31 December 2030

Study Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
	superficial siderosis), and intracranial haemorrhage, • prescriber and radiologist self-reported adherence to the risk minimisation practices. • prescriber knowledge of the prescriber checklist, including guidance on initial and subsequent treatment and recommendation for assessments before and during treatment with donanemab, • prescriber distribution of the patient card to patients prescribed donanemab for the first time, and • prescriber awareness and use of the CAP.			

Abbreviations: AD = Alzheimer's disease; ARIA = amyloid-related imaging abnormality; ARIA-E (cerebral oedema/effusion) = ARIA– oedema/effusions; ARIA-H (cerebral microhaemorrhage and superficial siderosis) = ARIA–haemorrhage/hemosiderin deposition; CAP = controlled access programme; EU = European Union; IRRs = infusion-related reactions; PBRER = periodic risk-benefit evaluation report; PSUR = periodic safety update report.

[a] Intracranial haemorrhage includes subdural haemorrhage, subdural haematoma, subarachnoid haemorrhage, cerebral haemorrhage, cerebral haematoma, haemorrhagic stroke, extradural haematoma, haemorrhage intracranial, intraventricular haemorrhage, thalamus haemorrhage, macrohaemorrhage, and cerebrovascular accident.

2.7.3. Risk minimisation measures

Table 35. Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
ARIA-E (cerebral oedema/effusion)	Routine risk minimisation measures: SmPC Sections 4.1, 4.2, 4.3, 4.4, 4.8, and Section 2 and 4 of the PIL. • Indication statement restricted to APOE ε4 non-carriers • Recommendations for monitoring and management of ARIA-E, including	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Follow-up form for ARIA and intracranial haemorrhage. Additional pharmacovigilance activities: Observational studies: • Registry-based observational study to characterise ARIA within a cohort of

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
	symptomatic cases, are included in SmPC Sections 4.2, 4.4, and Section 2 of the PIL. • Testing for APOE ε4 status should be performed prior to initiation of treatment with donanemab to inform the risk of developing ARIA. • Permanent discontinuation of donanemab treatment after serious ARIA-E or recurrent severe ARIA events is included in SmPC Sections 4.2 and 4.4. • Contraindications for use in cases of baseline imaging findings suggestive of increased risk for ARIA or intracerebral haemorrhage are included in SmPC Section 4.3 and Section 2 of the PIL. Legal Status: Restricted medical prescription Additional risk minimisation measures: • HCP educational material, including prescriber checklist • Patient Card • Controlled access programme	donanemab-treated patients in the EU. • Healthcare provider survey to assess the effectiveness of the donanemab additional risk minimisation activities in the EU.
ARIA-H (cerebral microhaemorrhage and superficial siderosis)	Routine risk minimisation measures: SmPC Sections 4.1, 4.2, 4.3, 4.4, 4.5, 4.8, and Section 2 and 4 of the PIL • Indication statement restricted to APOE ε4 non-carriers • Recommendations for monitoring and management of ARIA-H, including symptomatic cases, are included in SmPC Sections 4.2, 4.4, and Section 2 of the	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Follow-up form for ARIA and intracranial haemorrhage. Additional pharmacovigilance activities: Observational studies: • Registry-based observational study to characterise ARIA within a cohort of donanemab-treated patients in the EU. • Healthcare provider survey to assess the

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
	PIL. • Testing for APOE ε4 status should be performed prior to initiation of treatment with donanemab to inform the risk of developing ARIA. • Permanent discontinuation of donanemab treatment after serious ARIA-H or recurrent severe ARIA events is included in SmPC Sections 4.2 and 4.4. • Contraindications for use in cases of baseline imaging findings suggestive of increased risk for ARIA or intracerebral haemorrhage are included in SmPC Section 4.3, and Section 2 of the PIL. • Cautionary language on concomitant use of donanemab with antithrombotic medication, including anticoagulants and thrombolytics, is included in SmPC sections 4.4 and 4.5, and Section 2 of the PIL. Legal Status: Restricted medical prescription Additional risk minimisation measures: • HCP educational material, including prescriber checklist • Patient Card • Controlled access programme	effectiveness of the donanemab additional risk minimisation activities in the EU.
Hypersensitivity events (including IRR)	Routine risk minimisation measures: SmPC Sections 4.3, 4.4, 4.8 and, Sections 2 and 4 of the PIL • Contraindication for use in patients with prior history of hypersensitivity to donanemab is included in	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: Observational studies: • Secondary database study to characterise

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
	SmPC Section 4.3, and Section 2 of the PIL. • Recommendations for management of serious infusion-related reactions are included in SmPC Sections 4.3, 4.4, 4.8, and Sections 2 and 4 of the PIL. Legal Status: Restricted medical prescription Additional risk minimisation measures: • Controlled access programme	the safety, drug utilisation, and effectiveness of additional risk minimisation activities in donanemab-treated patients in the EU. • Registry-based observational study to characterise ARIA within a cohort of donanemab-treated patients in the EU.
Intracranial haemorrhage	Routine risk minimisation measures: SmPC Sections 4.2, 4.3, 4.4, 4.5, 4.8, and Section 2 of the PIL. • Testing for APOE ε4 status should be performed prior to initiation of treatment with donanemab to inform the risk of developing ARIA. • Contraindications for use in cases of baseline imaging findings suggestive of increased risk for ARIA or intracerebral haemorrhage are included in SmPC Section 4.3, and Section 2 of the PIL. • Permanent discontinuation of donanemab on identification of intracerebral haemorrhage greater than 1 cm is included in SmPC Sections 4.2 and 4.4. • Cautionary language on concomitant use of donanemab with antithrombotic medication, including anticoagulants and thrombolytics, included in SmPC Sections 4.4, 4.5, and Section 2 of the PIL. Legal Status: Restricted medical prescription	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Follow-up form for ARIA and intracranial haemorrhage. Additional pharmacovigilance activities: Observational studies: • Secondary database study to characterise the safety, drug utilisation, and effectiveness of additional risk minimisation activities in donanemab-treated patients in the EU. • Registry-based observational study to characterise ARIA within a cohort of donanemab-treated patients in the EU. • Healthcare provider survey to assess the effectiveness of the donanemab additional risk minimisation activities in the EU.

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
	Additional risk minimisation measures: • HCP educational material, including prescriber checklist. • Patient card • Controlled access programme	

Abbreviations: ARIA = amyloid-related imaging abnormality; ARIA-E (cerebral oedema/effusions) =ARIA–oedema/effusions; ARIA- H (cerebral microhaemorrhage and superficial siderosis) = ARIA–microhaemorrhage/hemosiderin deposition; EU = European Union; PIL = patient information leaflet; SmPC = summary of product characteristics.

2.7.4. Conclusion

The CHMP, having considered the data submitted in the application was of the opinion that due to the concerns identified with this application, the risk management plan cannot be agreed at this stage.

2.8. Pharmacovigilance

2.8.1. Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.8.2. Periodic Safety Update Reports submission requirements

Not applicable.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The originally claimed indication for donanemab is 'to slow disease progression in symptomatic adult patients with Alzheimer's disease (AD) in patients with evidence of amyloid beta pathology and a clinical diagnosis of either mild cognitive impairment (MCI) due to AD or mild AD dementia.' During the course of the MAA, the indication was restricted to exclude APOE-E4 homozygous patients, and further restricted to APOE-E4 non-carriers only. The now sought indication is *"Donanemab is indicated for the treatment of adult patients with a clinical diagnosis of mild cognitive impairment and mild AD dementia due to Alzheimer's disease (Early symptomatic Alzheimer's disease) who are apolipoprotein E ε4 (ApoE ε4) non-carriers with confirmed amyloid pathology (see section 4.4)."*

The proposed dosing is 700mg IV Q4W for the first three doses, followed by 1400mg Q4W. Treatment should be maintained until amyloid plaques are cleared. Treatment is limited to 18 months if monitoring of amyloid plaque clearance with a validated method is not possible.

Donanemab is a humanised immunoglobulin gamma 1 (IgG1) monoclonal antibody derived from the parental murine surrogate mE8 and was developed as a human IgG1 isotype to maximise the effector function in humans. Donanemab is directed against insoluble, modified, N terminal truncated form of amyloid beta (N3pG Aβ) present only in deposited brain amyloid plaques of AD patients. If approved, donanemab will present a new class of drugs.

AD is a progressive neurodegenerative disorder characterised by cognitive and functional decline. AD is the most common cause of dementia. In general, initial impairment in memory and executive dysfunction is followed by a decline in other cognitive domains and behavioural and neuropsychiatric symptoms. A person's ability to perform usual daily life activities will decrease with the progression of the disease. In the severe stages of AD, patients die due to AD-associated comorbidity (e.g., pneumonia). Patients' life expectancy is variable and depends on various factors like age at onset and

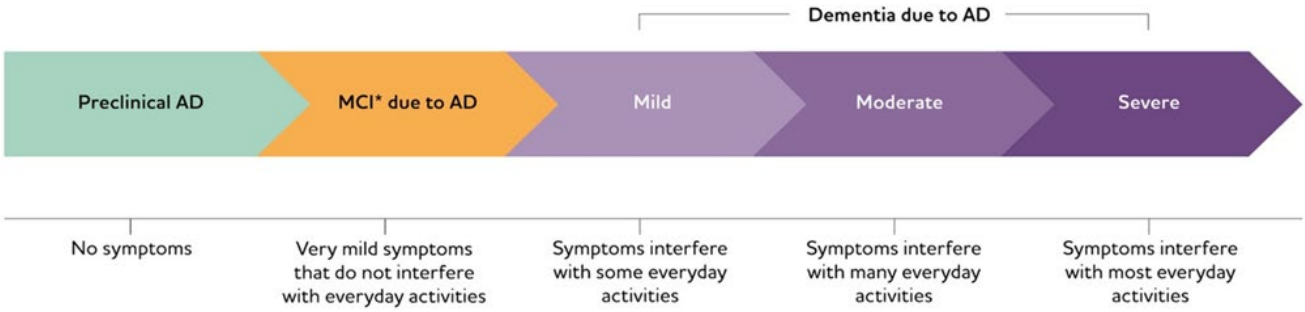
disease severity at the time of diagnosis. The apolipoprotein E (ApoE) ε4 allele is the strongest known genetic risk factor for AD.

AD is characterised biologically by the hallmark of two proteins: extra neuronal amyloid plaques and intra neuronal neurofibrillary tangles composed of hyperphosphorylated tau protein. Abnormal protein deposition occurs over a period of decades. This leads to neurodegeneration and significant subsequent cognitive decline, ultimately leading to death. According to the so-called amyloid hypothesis, accumulation of Aβ-peptide in the brain is driving AD pathogenesis. The rest of the disease process, including the formation of neurofibrillary tangles containing tau protein, is proposed to result from an imbalance between Aβ production and Aβ clearance. Until now, no amyloid targeting therapy showed an association with a comprehensive positive clinical outcome translated into a clinically relevant effect. As a result, the once widely embraced amyloid hypothesis is under discussion.

Current understanding of AD describes a biological and clinical continuum, extending from preclinical phases of disease evidenced only by neuropathology without clinical symptoms, through the early symptomatic phases (e.g., Mild Cognitive Impairment (MCI) due to AD / prodromal AD), and ultimately AD. Figure 17 displays the AD continuum. In MCI due to AD objective cognitive impairment (in general memory impairment) is present, but this does not interfere with activities of daily living. This is reflected in a CDR global score of 0.5. MCI due to AD is confirmed by a positive biomarker compatible with AD (i.e., abnormal levels of amyloid-beta). If the disease is interfering with daily living activities, a diagnosis of 'dementia' is set.

Over the past years the criteria to diagnose MCI due to AD and AD have been evolving. For a long time a clinical diagnosis of AD was mainly based on the exclusion of other conditions (McKhann criteria 1984). In the last decades criteria were several times revised in line with the insights gained on the pathophysiology of AD. A fundamental change was that AD was defined biological and not based on a clinical syndrome. Currently, the National Institute on Aging (NIA) and the Alzheimer's Association (AA) criteria are under revision again. One of the core principles still is that AD is defined biologically and not based on a clinical syndrome(s). In addition, an abnormality on one core biomarkers can be sufficient to diagnose AD; e.g., amyloid PET, CSF Aβ42/40, CSF P-tau181/Aβ42, CSF t tau/Aβ42, or "accurate" plasma assays. It is now also stated that these criteria are not intended as specific clinical practice guidelines, but rather criteria to inform diagnosis and staging of AD that reflect current science[3].

Figure 17. Alzheimer's disease continuum



*MCI is the acronym for mild cognitive impairment

Figure derived from ALZHEIMER'S ASSOCIATION REPORT - 2020 Alzheimer's disease facts and figures

[3] Revised Criteria for Diagnosis and Staging of Alzheimer's Disease: Alzheimer's Association Workgroup – Draft body Text as of October 9, 2023 Public Comment at alz.org/DiagnosticCriteria

3.1.2. Available therapies and unmet medical need

Approved treatment options for patients with mild to moderately severe AD are the cholinesterase inhibitors (donepezil, rivastigmine, and galantamine) and, for patients with moderate to severe AD, the N-methyl-D-aspartate antagonist; memantine. These agents provide symptomatic benefit with a limited duration of effect due to progression of the disease.

Several earlier clinical studies with other anti-Aβ monoclonal antibodies (bapineuzumab, solanezumab, crenezumab and gantenerumab) did not to meet their clinical endpoints. Recently, the MAA for aducanumab was withdrawn since the CHMP reached a negative opinion because the pharmacodynamic effect (i.e., reduction of brain amyloid load) was not translated into a clinically effect. Earlier, development of β-site amyloid precursor protein cleaving enzyme (BACE) inhibitors was stopped due to safety findings. Recently, lecanemab –an IgG1 monoclonal antibody directed against aggregated soluble and insoluble forms of amyloid beta- received a positive CHMP opinion for the treatment of MCI due to AD and mild AD.

Hence, there is an unmet medical need for an effective and safe treatment in AD in an ageing European population in which the prevalence of AD increases.

3.1.3. Main clinical studies

The single pivotal study of the MAA is phase 3 study AACI. The design of study AACI was conventional to assess efficacy of donanemab treatment, i.e. randomised double-blind placebo-controlled parallel group study with a duration of 76 weeks in 1736 randomised patients. By further restricting the indication to APOE-E4 non-carriers only a sample of approximately 29% (N = 510) of the population studied in the pivotal study remains. It is agreed that - taking the EMA guideline on subgroup analyses into consideration- the subgroup of APOE-E4 non-carriers can be judged as a credible subgroup.

In the original protocol, patients in the donanemab group were planned to receive 1400 mgQ4W. 43 (5%) Patients were randomly assigned to this dose and received this dose at initial infusion. Because of higher-than-anticipated serious ARIA-E, titration of three doses of 700mg Q4W was introduced after which the dose is 1400mg Q4W. Most patients received donanemab according to this dosing regimen.

Several protocol amendments were made for study AACI. The primary endpoint of the study was changed from the CDR-SB into the iADRS while the study was ongoing. The iADRS is a composite endpoint of a cognitive (ADAS-Cog13) and functional (ADCS-iADL) scale and was developed by the applicant. The scale ranges from 0-144, with a lower score implying more disease severity. At the time of the CHMP SA this endpoint was at discussion since it was not fully validated. In the end the CHMP endorsed the iADRS as primary endpoint. Therefore, (regulatory) experience with this scale is limited. In the assessment weight will be given to the CDR-SB, an established primary endpoint in AD trials. Other secondary endpoints are the ADAS-Cog13, ADCS-iADL and the MMSE. No outcomes assessing neuropsychiatric/ behavioural symptoms were included in the pivotal study, thus a possible effect of donanemab on neuropsychiatric symptoms/ behavioural cannot be established. Other important protocol amendments were the change from a phase 2 to phase 3 study and an increasing of the sample size. When the protocol amendments were made less than 7% of patients was randomised.

The patients were included according to reported gradual and progressive change in memory function (>6 months) reported by the patient or informant, an MMSE-score (20-28), and evidence of tau and amyloid deposition (as imaged by PET-scans). Based on their tau deposition patients were divided into the intermediate tau population (patients with low–medium tau pathology) or overall population (also the patients with high tau pathology). At week 24, 52 and 75 donanemab treated patients had a blind switch to placebo if amyloid reduction (on PET scan) was below a certain cut-off point.

Phase 2 study AACG was a randomised, double-blind, placebo-controlled study in 272 patients with MCI due to AD and mild AD with an intermediate tau load. Overall, the design was comparable with study AACI, except that the donanemab dose could be reduced to 700mg or placebo at week 24 or 52.

Limited data from the long-term extension of Study AACI were also submitted late in the procedure.

3.2. Favourable effects

Primary endpoint

On the iADRS, the mean difference in change from baseline in iADRS at week 76 between donanemab and placebo in the restricted population was 2.26 (95%CI: -0.44, 4.95). The mean difference in change from baseline in iADRS at week 76 between donanemab and placebo in the overall population was 1.90 (95%CI: 0.50, 3.29).

Secondary endpoints

On the CDR-SB, the mean difference in change from baseline at week 76 between donanemab and placebo in the noncarriers population was -0.56 (95%CI: -1.06, -0.07). The mean difference in change from baseline at week 76 between donanemab and placebo in the overall population was -0.53 (95%CI: -0.77, -0.29).

On the ADAS-Cog13, the mean difference in change from baseline at week 76 between donanemab and placebo in the restricted population was -1.25 (95%CI: -2.72, 0.22). The mean difference in change from baseline at week 76 between donanemab and placebo in the overall population was -0.79 (95%CI: -1.57, -0.02).

On the ADCS-iADL, the mean difference in change from baseline at week 76 between donanemab and placebo in the restricted population was 1.31 (95%CI: -0.47, 3.1). The mean difference in change from baseline at week 76 between donanemab and placebo in the overall population was 1.21 (95%CI: 0.35, 2.08).

For the MMSE, the mean difference in change from baseline at week 76 between donanemab and placebo in the restricted population was 0.24 (95%CI: -0.51, 0.1). In the overall population the difference was 0.24 (95%CI: -0.15, 0.63).

A reduction in cerebral amyloid beta was shown in patients treated with donanemab as compared to placebo. A total of 86% of donanemab-treated patients in the restricted population had amyloid clearance at 18 months. In the overall population this was 76% at 18 months. Exploratory biomarker data might imply an effect of donanemab on the downstream tau-related biomarkers, which would reflect the supposed causal pathophysiology of AD.

Restricted indication

During the course of the MAA, it was because of safety reasons post-hoc proposed to restrict the indication further by excluding APOE4 homozygous patients, and patients with baseline superficial siderosis, and >2 baseline microhaemorrhages. Now, the indication is further restricted to APOE-E4 non-carriers only. In the pivotal study 510 (29%) patients would represent the targeted population. Though, this sample is slightly older, the baseline cognitive measures and other demographic descriptives are comparable to those of the overall population. In this more restricted population the effect sizes show some increase in both low-medium tau and low-medium-high tau populations and when applying jump-to-reference imputation for missing data.

3.3. Uncertainties and limitations about favourable effects

Indication

Neither a clinical diagnosis of MCI due to AD or Mild AD, nor a CDR-score of 0.5-1 was required for entering the study. Rather the 'clinical' category was based on their MMSE score at screening. This method deviates from clinical practice. 96.7% of the participants had a CDR-G score of 0.5 or 1, which is in clinical practice consistent with MCI due to AD or mild AD dementia. The indication states clear that patients should have a clinical diagnosis of MCI due to AD or mild AD and that the decision to start treatment is not based on 'biological staging' of AD only.

Methodology

Analyses were performed on an evaluable efficacy set (EES) rather than the intention-to-treat (ITT) population. Restricting analyses to a subset with a post baseline measurement for the outcome available may have resulted in selection bias. Analysis methods used further seem to assume that missing outcomes after discontinuation are missing at random. This assumption is unlikely to be satisfied. MMRM analyses in the ITT population with post hoc sensitivity analyses using methods for handling missing data (jump-to reference-imputation) are expected to yield the most realistic estimates and have been provided.

There are three indications for poor study conduct: 1) 71.6% of all patients had at least 1 important protocol violation, 2) the inclusion of moderate AD patients, 3) the absence of (post)baseline values, with more missing data in the donanemab arm. This raises the question how well study conduct was monitored. Four study sites of the pivotal study and five sites of the phase 2 study have been inspected by the FDA, none of the inspections are classified as official action indicated. A GCP inspection was conducted for the pivotal study: AACI. After inspection of two sites (Poland and Canada) and the sponsor site, five major findings were reported. The deviations identified are not considered to impact the acceptability of the safety and efficacy data.

Outcomes

Although statistically significant differences between donanemab and placebo were found in the overall population including all APOE-E4 genotypes (except for the most conservative imputation strategy), there are uncertainties that limit the interpretation of the efficacy of donanemab as well as that the robustness of the data is questioned. This is the first study in AD with the iADRS as primary endpoint. This makes it hard to contextualise the findings. The 3.2 points difference proposed as minimal clinically important difference (MCID) for the iADRS to determine the samples size seems based on the Phase II study and not on clinical reasoning. This is of particular importance since the effect size in the ITT population is 2.52 in the intermediate tau population and 1.58 in the overall population, which is under 3.2 points. Literature regarding the MCID of the iADRS is limited. What is available was investigated by the applicant. Also, it is unclear whether the MCID applies to individual patients or to the group level. Moreover, also the MCID of the CDR-SB is not firmly established and heavily debated in the AD field[4,5,6]. The lack of long-term efficacy data after 76 weeks is another uncertainty. In addition, the support of the phase 2 study is limited as the results are less consistent in the intermediate tau population than the results in this population in the phase 3 study.

[4] Lansdall C.J. et al. (2023). Establishing Clinically Meaningful Change on Outcome Assessments Frequently Used in Trials of Mild Cognitive Impairment Due to Alzheimer's Disease. J Prev Alz Dis; 1(10):9-18; http://dx.doi.org/10.14283/jpad.2022.102

[5] Petersen RC et al. (2023) Expectations and clinical meaningfulness of randomized controlled trials. Alzheimer's Dement.;19:2730–2736. https://doi.org/10.1002/alz.12959

[6] Van Dyck (2023). Letter: Disease severity and minimal clinically important differences in clinical outcome assessments for Alzheimer's disease clinical trials. Alzheimer's & Dementia: Translational Research & Clinical Interventions. https://doi.org/10.1002/trc2.12388

Hazard ratios of progression in terms of points decline on outcome measures/ at the CDR-global in the restricted population are also provided. Although these show high ratio's with statistically significant differences, the absolute differences between placebo and donanemab (irrespective of the included population and imputation methods) are not so impressive. The absolute difference in number of responders (events) is for most comparisons around 10%.

Throughout the dossier, it is consistently found that in patients with a higher tau load the effects are lower.

Clinical relevance

The clinical relevance of the findings in this single pivotal study with limited efficacy data after 76 weeks has not been sufficiently substantiated. The applicant provided cumulative responder curves of change on the iADRS as well as for the CDR-SB for the duration of the placebo-controlled phase. These indicate that at several cut-off points for different outcomes the maximum difference between placebo and donanemab is 12% more patients being a responder on a certain cut-off. Concordance tables with the number of patients reaching the MCID, or not on both the iADRS and CDR-SB were provided for the overall population. These indicated that the concordance between these measures is considered moderate. Several issues in the dossier hamper the interpretation of the results in context of clinical relevance for both populations.

In AD an effect on both cognition and functional outcome needs to be established. A domain analysis showed that the overall composite score of the CDR-SB was not dominated by one of the two dimensions of the scale.

Estimated time-saved in the restricted population ranged from 1.1 months for ADAS-Cog to 2.7 months for CDR-SB. In the overall population estimates ranged from 0.8 months for ADAS-Cog to 3.1 months for CDR-SB. It is noted that the estimated time-saved is missing for the MMSE. This has to be placed in the perspective of a in general slowly progressive disease with a median duration of 6.2 years (range 6.0-6.5 years) after a diagnosis of AD in the dementia phase[7]. If the prodromal (MCI due to AD) and preclinical phase are added the estimate of total disease duration is 20 years.

Single pivotal study

This MAA is based on a single pivotal study with a subsample of the original included population. The area of AD and anti-amyloid agents is one of failed studies. Hence there is a particularly strong need to have a clear demonstration that targeting existing amyloid plaques can delay the progressive disease course of AD. Relying on one pivotal study has a risk of false positive conclusions. While the study was running, several modifications that may have affected study integrity were made. Considering this all, a study that replicates the findings of the pivotal phase 3 study of donanemab in MCI due to AD and mild AD seems essential. In the Phase 2 study on the primary endpoint a difference was found between placebo and donanemab. Though, this was not the case for almost all secondary endpoints. The phase 2 study is considered exploratory and in that respect of limited support for the single pivotal phase 3 study.

Long term efficacy

The treatment paradigm proposed for donanemab and the mechanism of action directed against plaques raises questions on whether the benefit of treatment is preserved after discontinuation. The limited preliminary LTE data submitted late in the procedure are difficult to interpret and do not substantially address this concern, as outlined above.

7 Scheltens P., et al., Alzheimer's disease. The Lancet (2021) https://doi.org/10.1016/S0140-6736(20)32205-4

In conclusion, and considering the magnitude of effect and the uncertainties on the long-term effect, a clinical meaningful level of efficacy has not been demonstrated.

3.4. Unfavourable effects

The adverse event profile of donanemab is dominated by amyloid-related imaging abnormalities (ARIA). In the pivotal study AACI-PC, amyloid-related imaging abnormalities -oedema/effusion (ARIA-E) occurred in 24.0% of donanemab-treated patients compared to 2.1% in controls. Amyloid-related imaging abnormalities -microhaemorrhages and haemosiderin deposits (ARIA-H) occurred in 31.4% of donanemab-treated patients compared to 13.6% in placebo. Within ARIA-H, microhaemorrhage (26.8% vs. 12.5%, resp.) and superficial siderosis of the CNS (15.7% vs. 3.0%, resp.) occurred more often in the donanemab group compared to controls. In addition, hypersensitivity events occurred in 10.4% of donanemab-treated patients compared to 0.9% of controls.

The overall incidence of serious AEs was higher in the donanemab group (17.4%) compared to controls (15.8%), and the difference was mainly driven by serious events of ARIA-E and ARIA-H; serious ARIA was not reported in the placebo group.

More patients died in the donanemab group (n=16, 1.9%) than in the placebo (group n=10, 1.1%). Three deaths under donanemab were attributed to ARIA-E and/or ARIA-H. In All Dona, three additional deaths were (at least possibly) attributed to donanemab (due to ARIA [n=1] and/or macro-haemorrhage [n=2]). In dosing study AACQ, a seventh treatment-associated death with ARIA occurred. Six fatal cases all concerned APOE4 heterozygote patients, and one concerned an APOE4 non-carrier patient.

ARIA and hypersensitivity events (including injection-related reactions [IRR] and anaphylaxis) were considered adverse events of special interest (AESI).

ARIA

More than half of initial ARIA-E occurred by the third infusion, and all initial events occurred within the first year. Based on MRI, 44% of ARIA-E events concurred with ARIA-H events. ARIA-E took a median of two months to resolve radiographically (mean of 70 days). Although the majority of patients (75%) had one event of ARIA-E, approximately a quarter of patients with ARIA-E had recurrent events, with up to four events of ARIA-E (in six patients). ARIA-E events seemed to fully diminish over the course of 18 months.

ARIA-E was mostly mild (28.7%) to moderate (64.4%) in MRI severity, but in 6.9% of cases severe. Similarly, most ARIA-E events were non-serious (93.6%), but in 6.3% of patients with ARIA-E (n=13) the event was serious. Almost all serious ARIA-E (12/13; 92.3%) events were symptomatic, three serious events were fatal, and no patient had recurrent serious ARIA-E. In the placebo group, no severe or serious events of ARIA-E occurred.

Around a quarter (25.4%) of donanemab-treated patients with ARIA-E had symptoms (i.e., 6.1% of all donanemab-treated patients), mostly headache and confusion, but also seizures. In 85% of these patients (44/52) symptoms resolved, while 15% of patients with symptomatic ARIA-E continued to have clinical symptoms, including seizure and aphasia, also after radiographic resolution. Most serious or symptomatic ARIA-E events were treated with supportive therapy, usually corticosteroids, although their effect on ARIA duration and resolution was not substantiated.

Most initial ARIA-H events occurred within the first six months of treatment, but initial events were also reported after more than 1 year of treatment. It is estimated that around two thirds of patients with ARIA-H experienced one ARIA-H event, while one third of patients experienced two to six events.

Recurrent events were generally more severe. Initial and recurrent events occurred throughout the study, although less frequently later on, and had not weaned at 18 months.

Most ARIA-H events were mild (47.2%) or moderate (19.5%) in severity. A third of patients (33.3%) experienced severe ARIA-H, more often due to superficial siderosis of CNS than due to microhaemorrhage; 40% of all superficial siderosis of CNS were radiographically severe. Most ARIA-H events were non-serious, except in four patients (1.5% of patients with ARIA-H). Of these, three concurred with serious ARIA-E, and two were fatal.

Based on extended search criteria for macro-haemorrhage, 11 [1.3%] donanemab-treated participants had a (macro) haemorrhagic lesion versus 7 [0.8%] of placebo-treated participants.

The dosing actions taken with donanemab in response to events of ARIA-E and/or ARIA-H did not always follow the protocol, which is more or less in line with the proposed SmPC (i.e., continue or temporarily suspend dosing, depending on ARIA severity and symptomatology), specifically for moderate to severe ARIA and symptomatic ARIA-E. In total, 10% of donanemab-treated patients stopped treatment due ARIA-E, and 3.7% of donanemab-treated patients stopped treatment due to ARIA-H.

APOE ε4 carrier status and specific baseline MRI findings (presence of microhaemorrhage, superficial siderosis) were associated with increased frequency of ARIA. The frequency of ARIA was highest in homozygote carriers, followed by heterozygote carriers, and non-carriers. ARIA frequency more or less halved per APOE ε4 allele less. Fatal events did not appear associated with APOE ε4 carrier status.

Restricted population

When APOE4 homozygote and heterozygote carriers (i.e., patients at highest risk of ARIA) are excluded from the target population, ARIA incidence is lower compared to the overall population, with ARIA occurring in a quarter of non-carrier patients (24.7%; ARIA-E: 15.7%, ARIA-H: 18.8%). Also severe, serious and symptomatic ARIA is reduced, with symptomatic ARIA occurring in 4.3% of patients (3.9% ARIA-E, 0.4% ARIA-H) and serious ARIA in 0.8% of patients. Timing of ARIA and ARIA recurrence rates are largely comparable to the overall population.

The incidence of macro-haemorrhagic events in the restricted population remains higher under donanemab compared to placebo (2.0% vs. 0.4%), and mainly concerned subdural and subarachnoid haemorrhages. Serious events of macro-haemorrhage occurred in 1.6% of patients in the restricted population.

One treatment-related death (due to ARIA-H and haemorrhagic stroke) occurred in an APOE4 non-carrier patient with baseline SS and a history of hypertension.

Hypersensitivity

Immediate hypersensitivity events (10.4%) mostly concerned IRR (8.7%). Also anaphylactic reactions (0.3%) and angioedema/urticaria (0.3%) were reported. Hypersensitivity-associated symptoms included erythema, chills, nausea/vomiting, sweating, difficulty breathing/dyspnoea, and elevated blood pressure.

The majority of initial events occurred by the fourth infusion (71%). Most events occurred during treatment administration (82.8%), were attributed to donanemab, mild to moderate in severity, and resolved within 24 hours. In total, 4.0% of IRRs, half of angioedema/urticaria events, and 20% of hypersensitivity events were reported as severe. Three serious hypersensitivity events occurred under donanemab: an infusion-related hypersensitivity reaction, an IRR, and urticaria. Events resolved the same or the next day.

Almost half of all patients with hypersensitivity events permanently discontinued treatment with donanemab (3/3 with anaphylactic reaction; 31/72 with IRR; and 4/10 with hypersensitivity events). Prophylactic mediation or slowed infusion did not prevent a subsequent IRR upon rechallenge infusion. Subsequent IRRs were, in most cases, not more severe than the initial event.

In the restricted population, hypersensitivity events occurred in 7.8% of patients, which is in line with the overall population.

Anti-donanemab antibodies (ADA) were present in 88.1% of donanemab-treated patients (neutralizing antibodies all ADA positive patients). Higher ADA titres were associated with a higher incidence of IRR.

3.5. Uncertainties and limitations about unfavourable effects

Deaths

In AACI-PC, more patients died in the donanemab group than in the placebo group. Three deaths in AACI-PC were due to donanemab-related ARIA-E and/or ARIA-H. Two of the three deaths concerned APOE4 heterozygote carriers, and another concerned an APOE4 non-carrier patient with baseline SS.

In the clinical programme of donanemab, 7 treatment-associated deaths occurred. All concerned APOE4 heterozygote carriers, except one, that concerned a non-carrier (in AACI-PC) with baseline SS. Six of the 7 deaths concerned events of ARIA-E and/or -H, and one concerned a macro-haemorrhagic event without ARIA. One of the 7 deaths due to ARIA and/or haemorrhage was previously deemed preventable, had the patient not been re-dosed after an event of asymptomatic severe ARIA. Although, obviously, not all patients with severe ARIA died, this example was one of the arguments for implementation of permanent stopping rules. The applicant proposed stricter stopping rules for serious ARIA and for recurrent severe ARIA events. However, treatment (dis)continuation in case of severe ARIA will be a matter of clinical judgement, for which experience and training is considered essential, but not necessarily sufficient to prevent fatalities.

Two fatal cases concerned patients who received thrombolytic therapy in the presence of ARIA-E. The high mortality with concomitant thrombolytic therapy (2 out of 4 patients died) remains a large concern. The proposed warnings with regard to a correct diagnosis and possible alternative treatment approaches can be endorsed, pending some further amendment.

In the post-marketing setting, an additional ARIA-associated fatal case (unknown APOE4 carrier status) was referred to.

ARIA

Most donanemab-treated patients with symptomatic ARIA-E received supportive therapy, but this did not have an effect on symptom duration or radiographic or symptom resolution. A total of 15% (n=8) of donanemab-treated patients continued to have clinical symptoms. Unresolved ARIA-E symptoms were aphasia; seizure; dementia; somnolence and confusional state; and balance disorder and diplopia. Radiographic resolution of ARIA-E was reported in several patients, which implies there may be long-term sequelae of ARIA-E, although they may be rare. At the same time, ARIA symptomatology may overlap with symptoms of AD, which may complicate identification. To evaluate whether ARIA-related symptoms may have been masked by symptoms of AD, assessment of AEs and cognitive status prior to and after an ARIA event, and comparison with ARIA-free patients, was requested. No notable differences in AE reporting indicative of such masking were identified, nor a difference in cognitive status in patients with or without ARIA.

Based on extended search criteria, macro-haemorrhagic events occurred more often in donanemab-treated patients than in placebo patients (1.3% [n=11] vs. 0.8% [n=7], resp.; All Dona: 1.3%

[n=35]). More than half of cases had concurrent ARIA-H and/or ARIA-E (All Dona). Around 9% (n=3 in all Dona) concerned fatal events related to donanemab. Considering this higher incidence, the causal relationship with donanemab in several patients, the mechanism of action and the known class effect, macro-haemorrhage was requested to be included as an ADR of donanemab. The applicant proposed to include intracranial haemorrhage instead, which is agreed.

Although antithrombotic use was reported not to impact the frequency of ARIA-H events, concomitant antithrombotics (including anticoagulants) could potentially be associated with more severe or serious ARIA-H, or macro haemorrhagic (cerebral or intracranial) events.

ARIA mitigation

Dosing actions taken in response to ARIA in AACI-PC did not always follow the protocol, which is more or less (but not fully) in line with the proposed SmPC (i.e., continue or temporarily suspend dosing, depending on ARIA severity and symptomatology). Based on the provided data, assessment of the most appropriate dosing advice in case of ARIA is not straightforward. Data do not necessarily indicate that the proposed recommendations lead to better resolution and recurrence rates than alternative dosing options. Considering that the majority of patients were treated according to the study protocol's instructions, most recommendations were accepted. In response to remaining concerns, the applicant has amended the recommendations for dosing, re-assessment of risk factors, and permanent stopping criteria. These are considered acceptable now.

Initially, the recommended monitoring for ARIA was an MRI within one year prior to initiating treatment, and prior to second dose, prior to dose increase, and prior to the seventh dose. A more recent MRI prior to treatment (i.e., within 6 months) was agreed on, based on the observed changes in MRI findings over one year. Further, a peak of ARIA events occurred prior to 3rd infusion, and therefore an additional MRI prior to 3rd infusion was recommended for all patients. The added value of the intensified MRI monitoring for the restricted population of non-carriers is less clear, and therefore, the MRI monitoring schedule used in the pivotal trial is deemed acceptable (i.e., without an extra MRI prior to third dosing). Considering the number of new (severe) cases of ARIA-E and ARIA-H up to 1 year of treatment, MRI after 7th infusion was requested to be reconsidered. However, as ARIA incidence is much lower after 6 months of treatment, and the current recommendations in fact allow for an MRI assessment at any time, if clinically warranted, an obligatory MRI was not deemed necessary, which can be accepted.

The effectiveness and feasibility of MRI monitoring in clinical practice cannot sufficiently be addressed at this stage, and a Controlled Access Programme ensuring that access is granted only when appropriate monitoring can be planned is deemed necessary.

APOE ε4 carrier status and specific baseline MRI findings (presence of microhaemorrhage, superficial siderosis) were the factors most strongly associated with increased frequency of ARIA events in the clinical studies. For specific baseline MRI findings, contraindications are proposed (see later). Furthermore, the applicant initially proposed to exclude the patients at highest risk of ARIA, i.e., APOE4 homozygote carriers, from treatment with donanemab. However, the remaining population of APOE4 heterozygote carriers and non-carriers remained at high risk of ARIA and, importantly, ARIA-associated fatal events were not significantly reduced. The applicant proposes to restrict the target population to APOE4 non-carriers only. All APOE4 carriers will thus be excluded from treatment with donanemab. The remaining target population is 29% of the study population. In the restricted population, ARIA incidence is reduced by 12~% compared to the initial target population. In absolute terms it is still very high, with around a quarter of patients (twice as much as with placebo) experiencing ARIA (any ARIA: 24.7% vs. 36.8, resp.; ARIA-E: 15.7% vs. 24.0%, resp.; ARIA-H: 18.8% vs. 31.4%, resp.; serious ARIA: 0.8% vs. 1.6%, resp.; symptomatic ARIA-E: 3.9% vs. 6.1%, resp.). The incidence of macro-haemorrhage also remains higher under donanemab (2.0% vs. 0.4%

with placebo), with serious macro-haemorrhagic events in 1.6% of patients. One of the seven deaths related to treatment occurred in the restricted population of non-carriers. A link between APOE4 carrier status and fatalities is not apparent for donanemab. Treatment-related fatalities may not necessarily be prevented with the current measures, e.g., in case patients have concurrent cardiovascular co-morbidities and/or receive antithrombotic medications, in particular thrombolytic therapy. Or, in case the safety measures are not strictly applied by the treating physicians.

Initially, no contra-indications were proposed by the applicant, although there were several exclusion criteria in the pivotal study based on grounds of safety, i.e., due to increased risk of ARIA and/or macro haemorrhage (pre-existing ARIA-E, >4 microhaemorrhages, >1 area of superficial siderosis, any macro-haemorrhage, or severe white matter disease). Factors that can be indicative of cerebral amyloid angiopathy. One of the seven fatal cases related to donanemab occurred in a patient (APOE4 non-carrier) with baseline SS. Furthermore, patients who developed macro-haemorrhage or 'severe white matter disease' during the course of the studies were never re-dosed. Based on these safety grounds, the applicant agreed to update the list of contra-indications to include: 'Baseline MRI findings of prior intracerebral haemorrhage greater than 1 cm, >4 microhaemorrhages, superficial siderosis, or vasogenic oedema (ARIA-E), or other findings, which are suggestive of cerebral amyloid angiopathy (CAA)' and 'severe white matter disease'.

Furthermore, to optimise the safety of donanemab, the applicant proposes a controlled access programme (CAP). It is acknowledged that the programme may help health care professionals to adhere to certain risk minimisation measures, e.g., select the correct patients, and inform patients about the risks. However, it should be noted that a CAP does not change the risks seen with donanemab; even when measures are applied correctly, a substantial group of patients in the target population will experience ARIA, including serious and fatal events. Moreover, the effectiveness and feasibility of MRI monitoring in clinical practice is not yet sufficiently addressed and will need to be followed up in post-authorisation studies (PASS).

Long-term safety

There appears to be a lag time between plaque clearance and changes in whole brain volume, which suggests that these changes cannot solely be explained by plaque removal. Part of the observed brain volume changes (ventricular volume) may be related to ARIA-E. A maximum treatment duration of 18 months is now proposed by the applicant, and long-term (post-treatment) consequences of ARIA, including (clinical relevance of) brain volume changes, should be further investigated in a PASS

Hypersensitivity

Almost half of all patients with hypersensitivity events permanently stopped treatment with donanemab. For patients who did re-start treatment, prophylactic medication or slowed infusion did not prevent a subsequent IRR upon rechallenge infusion. More than half of patients with a (mostly mild) IRR were rechallenged, with severity and symptoms usually similar to that of initial events.

Conclusion

In sum, the safety profile of donanemab, which is dominated by ARIA, is worrisome. Although the majority of ARIA events appear mild to moderate in MRI severity and are asymptomatic, part of the patients experience serious events and/or have clinical symptoms, and also fatal cases of ARIA and macro-haemorrhage were reported. In a restricted population of APOE4 non-carriers, the safety profile improved compared to the overall population. Though, ARIA incidence remains substantial; ARIA occurs in a quarter of donanemab-treated patients, twice as much as under placebo. Although less common compared to the overall population, symptomatic ARIA (4.3%) and serious ARIA (0.8%) were also observed in the restricted population. One ARIA-related fatal event occurred in a non-carrier. This

patient had baseline SS, which is proposed as contraindication. Though this measure is endorsed, it does not take away the concern that treatment-related deaths may not be preventable in the subgroup of non-carriers either, for example in case of (e.g., cardiovascular) co-morbidities, or when antithrombotic medication is used (e.g., thrombolytic therapy), or in case risk minimisation measures are not strictly applied by the treating physicians. The effectiveness and feasibility of the risk minimisation measures in clinical practice also remains of concern. Thus, the CHMP considers that safety of donanemab is not sufficiently demonstrated.

3.6. Effects Table

Table 36. Effects table for donanemab to slow disease progression in APOE-E4 non-carrier adult patients with MCI or mild dementia due to Alzheimer's disease (AD)[#] (database lock: 28-4-2023)

Effect	Short Description	Unit	Donanemab	Placebo	Uncertainties/ Strength of evidence	References
Favourable Effects*						
iADRS	Mean Δ from baseline at week 76		-13.58	-15.84	SoE: Primary endpoint. Low-medium-high tau population: difference between donanemab and placebo 2.26 (95%CI; -0.435; 4.952), p=0.10. Unc: clinical relevance of findings	Study AACI, applicant's response document
CDR-SB	Mean Δ from baseline at week 76		2.17	2.73	SoE: Important secondary endpoint. Low-medium tau population: difference between donanemab and placebo -0.56 (95%CI; -1.064; -0.065), p=0.027. Unc: Clinical relevance of findings	Study AACI, applicant's response document
Unfavourable Effects						
Treatment-related deaths	Incidence of treatment-related deaths	n	1	0	SoE: overall pop: n=3 in AACI, 3 additional related deaths due to ARIA and/ or macro-haemorrhage in All Dona. Additional death in Study AACQ (total related fatalities in clinical programme: n=7). Post-marketing: 1 additional death. Unc: preventability	Study AACI
ARIA-E[$]	Incidence of ARIA-E	%	15.7	0.8	Unc: Effect of supportive treatment; Long-term effects post treatment	Study AACI

Effect	Short Description	Unit	Donanemab	Placebo	Uncertainties/ Strength of evidence	References
ARIA-H[$]	Incidence of ARIA-H: -Overall -Micro haemorrhage -Superficial siderosis CNS	%	 18.8 15.3 7.5	 11.2 10.8 1.2	Unc: Long-term effects post treatment	Study AACI
Macro-haemorrhage	Incidence of macro-haemorrhage	%	2.0	0.4	SoE: 1.3% in All Dona; MoA; observed with other anti-amyloid therapies; ≥3 events related to donanemab. Unc: MRI misreadings	Study AACI
IRR	Incidence of IRR	%	7.8	n.r.	SoE: 40-50% of patients with IRR/hypersensitivity permanently stop treatment (also in All Dona). Prophylaxis not effective (All Dona).	Study AACI

Abbreviations: ARIA-E = Amyloid Related Imaging Abnormality - oedema/effusions, ARIA-H = Amyloid-related imaging abnormality-microhaemorrhage and haemosiderin deposits, CDR-SB = Clinical Dementia Rating Scale – Sum of Boxes, iADRS = integrated Alzheimer's Disease Rating Scale, IRR = infusion-related reactions, SoE = strength of evidence, Unc = uncertainty.

#The restricted indication with APOE-E4 non-carriers only contains a sample of approximately 29% (N = 510) of the population studied in the pivotal study.
* MRMM analyses performed in ITT (intent-to-treat) population that included all randomised participants; post hoc sensitivity analyses using methods for handling missing data (jump-to reference-imputation).
$ All ARIA: 24.7% donanemab vs. 12.0% placebo; serious ARIA: 0.8% donanemab [0.4% ARIA-E, 0.4% ARIA-H] vs. 0% placebo; symptomatic ARIA: 4.3% donanemab [3.9% ARIA-E, 0.4% ARIA-H] vs. 0.4% placebo [ARIA-H].

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Importance of favourable effects and the associated uncertainties

The field of AD has a history of many failed studies including agents based on the amyloid hypothesis. This implies that there is no established association between cerebral amyloid reduction and clinical outcomes that are translated into a clinically relevant effect. This MAA contains a single pivotal study. In case of a single pivotal trial, the data have to be particularly compelling with respect to internal and external validity, clinical relevance, statistical significance, data quality, and internal consistency (points to consider on application with 1. Meta-analysis, 2. One pivotal study, EMA; PMP/EWP/2330/99). Whereas in this points to consider it is stated that there is no formal requirement to include two or more pivotal studies in the phase III programme, it is also stated that there are many reasons why it is usually prudent to plan for more than one study in the phase III programme. These include among others limiting or unconvincing phase I and phase II data, and a therapeutic area with a history of failed studies.

By further restricting the indication to a subgroup of APOE-E4 non-carriers only approximately 29% of the population studied in the pivotal study remains. Though, this sample is slightly older, the baseline

cognitive measures and other demographic descriptives are comparable to those of the overall population. The subgroup of APOE-E4 non-carriers can be considered as a credible subgroup.

There is a strong need to have a clear demonstration that targeting existing amyloid plaques can delay the progressive disease course of AD, also in terms of clinical relevance. The pivotal study seems to fall short in this perspective. Although a reduction in cerebral amyloid load was seen after donanemab treatment, the small effect sizes observed limits the interpretation of the data in terms of clinical relevance, also in the restricted population. There were several major changes made to the analysis based on CHMP request, as data were initially not analysed in the ITT population and a missingness at random assumption was made for outcomes after permanent study discontinuation and death. This assumption is unlikely to be satisfied. Results of the analyses in the ITT population under a preferred method of missing data handling (imputation using a jump to reference imputation for missing outcomes) showed more realistic, but smaller and less compelling effect sizes. Another limitation is the very limited long-term efficacy data. This is a concern, in a progressive disease with a duration of more than 18 months, also in light of the posology and mechanism of action of donanemab.

Throughout the dossier it is found that in patients with a high tau load, the effects are even smaller.

Importance of unfavourable effects and the associated uncertainties

The incidence of ARIA under donanemab is high, especially in a population of early AD patients. Although most patients experience one asymptomatic event of (radiographically) mild to moderate ARIA, there is also a number of patients with more severe and/or unresolved symptoms. Most worrisome, several fatal cases due to ARIA and/or macro-haemorrhage related to donanemab treatment were reported.

The applicant extensively updated the risk management measures for ARIA, which is fully appreciated. Specifically, the exclusion of all APOE4 carriers from the indication has a positive impact on ARIA incidence and ARIA-related deaths. Still, ARIA incidence is substantial in this small subgroup of APOE4 non-carriers, and concerns for fatalities remain.

The effectiveness and feasibility of the proposed monitoring and risk minimisation measures in clinical practice remains an ongoing major concern, specifically in case there are challenges with the full implementation of the proposed risk minimisation measures (among others, genetic testing, periodic monitoring MRIs), or when the treated population has more co-morbidities (including concurrent medications). Post-authorisation safety and efficacy studies may be imposed.

In addition, hypersensitivity events occur commonly, and treatment withdrawal due to these events is very high. Recurrence of hypersensitivity events upon retreatment cannot be mitigated, but subsequent IRR/hypersensitivity events were in most cases not more severe than the initial event.

3.7.2. Balance of benefits and risks

The unmet medical need for a disease-modifying treatment of AD is acknowledged. Approved treatments have limited effect on cognitive decline.

The small effect sizes found in the APOE4 non-carriers in the single pivotal study are – also in light of the SAG outcome – considered small, and clinical relevance has not been demonstrated. The preliminary long-term efficacy data is limited and inconclusive, and the posology and mechanism of action raises questions about the effect (and maintenance thereof) beyond 18 months.

Although for most patients, ARIA was a single, asymptomatic mild event, some patients experienced severe or serious and/or symptomatic ARIA. Most worrisome, ARIA-related deaths, sometimes with macro-haemorrhagic events, occurred, also (once) in the restricted population of APOE4 non-carriers.

Although the updated monitoring and risk minimisation measures, including the proposed restriction of target population, improve the safety profile of donanemab and can be agreed, ARIA incidence is still substantial, and concerns for potentially fatal events remain. The effectiveness and feasibility of MRI monitoring is questioned.

To conclude, even for the small population of APOE4 non-carriers, ARIA incidence remains substantial, and serious and symptomatic events still occur. As for the broad indication, the effect sizes are small and the long-term efficacy not demonstrated. The small effects that are seen in this subset of patients are of uncertain clinical relevance and do not outweigh the risk of potentially fatal events of ARIA in a population of APOE4 non-carriers.

3.7.3. Additional considerations on the benefit-risk balance

SAG Neurology

On December 5 2024, a SAG Neurology meeting was convened upon request of the CHMP. Next to the SAG members, additional experts were present. The following issues were discussed:

1. **The SAG is asked to comment on the clinical relevance and meaningfulness of the differences in the primary and key secondary endpoints for the early AD patient (MCI due to AD and mild AD):**

    a. **The difference in IADRS (primary endpoint) in the ITT population is estimated 2.52 (95%CI: -1.12, 3.93) in the low-moderate tau group, and 1.58 (95%CI: 0.19, 2.97) in the low-moderate-high tau group.**

The SAG-N experts considered by consensus that the magnitudes of the above mentioned endpoints are not clinically meaningful. The experts expressed different opinion statements in support to it. The experts noted that IADRS scale is not widely used so the experience is still limited, but MCID estimated in the literature are higher than the estimated mean difference (5 points in MCI due to AD and 9 points in mild AD dementia Wessels AM, et al Alzheimers Dement. 2022;8(1):e12312).

Some of the experts expressed the view that data do not clearly support that there a lasting effect on the progression of the condition such that the difference would grow over time. Some experts stated that the difference between treatment arms occurs early in the study. Later the curves for most clinical outcomes run almost in parallel, not supporting disease modification. Other expert expressed that longer follow-up would have been needed to assess lasting effects. The higher drop-out in the donanemab group (7% more than in the placebo group) was discussed by some experts as a point that may have contributed to the difference between the arms because of selective drop-out of those with adverse events and doing worse in the intervention arm.

The experts also discussed the potential role of functional unblinding and concluded that it may have influenced the effects on patient and caregiver-reported outcomes, but not on objective tests.

Some SAG-N experts considered that efficacy should have been evaluated in terms of percentage of the absolute change from baseline. Most experts indeed were of the opinion that effect should primarily be expressed in absolute terms, and not in relative terms i.e. of percentage of decline prevented. Few experts expressed that the concept that 20% slowing of decline placebo reflects clinical relevance was not agreed on, because 20% of a small effect is not necessarily clinically relevant. One SAG-N expert questioned the validity of the analysis based on results available in the literature.

One of the patients' representatives expressed the view that the delay of progression that has been observed with donanemab is modest and would not overweigh the burden of treatment.

b. The difference in CDR-SB (key secondary endpoint) in the ITT population is estimated -0.51 (95%CI: -0. 78, -0.23) in the low-moderate tau group, and -0.47 (95%CI: -0.72, -0.23) in the low-moderate-high tau group

The SAG-N experts considered by consensus that the above magnitudes are not clinically meaningful. The experts discussed how the MCID for CDR-SB has not been firmly established. While 0.5 has been reported by some authors - which matches with 0.5 being the lowest possible change in a scale measuring disease severity-, higher values deriving from anchor-based studies are widely acknowledged (i.e. 1 point for MCI and 1.5-2 point for mild AD). Subgroup analysis as reported in the supplement, using the EES population (combined), show 0.29 point in MCI and 0.68 in mild dementia, well below the reported MCID in the literature.

2. The SAG is asked to comment on the clinical relevance of ARIA-Es and ARIA-Hs and the manageability of these imaging abnormalities in clinical practice:

a. Does the SAG consider that the risk minimisation measures as proposed by the Applicant are sufficient to handle this risk, also in case of concomitant use with thrombolytics by some patients as this could potentially be associated with more severe or serious ARIA-H, or macro haemorrhagic (cerebral or intracranial) events?

The SAG-N acknowledged that the currently proposed risk minimisation measures (RMM) are reasonable (MRI monitoring, specialised centre, controlled access programme, healthcare professional educational material and patient card). Even if fully implemented, some experts considered that these may be still insufficient to fully manage for the risk of ARIA. For the MRI monitoring, the SAG-N experts questioned the feasibility to be fully implemented in Europe and questioned the acceptability from the patient’s perspective.

In connection with these measures, the SAG-N questioned the feasibility to implement a restriction of the indication based on results of the Tau-PET (i.e. exclusion from the indication in those with high levels) in Europe.

With regards to thrombolytics, the SAG-N experts noted that a patient card might not be an effective RMM because of the emergency room setting and the neurological status of the patient (e.g. aphasia due to stroke, cognitive impairment) may impede its effective use. Further, the use of thrombolytics appears in an emergency context (i.e. ischemic stroke) in which it is not feasible to spare time for discussing the matter. A discussion on the high risk of ARIA or macrohaemorrhage when acute stroke is treated with thrombolytics is needed and should be planned at the time of the prescription of Donanemab. Some experts consider this a very complex decision for patients. The SAG-N experts noted that the increased risk of ARIA in context of concomitant use with thrombolytics is particularly worrisome as the number of patients at risk of using these medications is growing.

b. Does the SAG consider that there are subgroups of patients particularly harmed by the treatment (e.g. APOE4 carriers, specific baseline MRI findings like white matter disease indicative for CAA, or macro-haemorrhage)? If there are such populations, what measures are considered warranted before initiation of the treatment in order

to properly mitigate the risk of ARIA; i.e., a mandatory testing for APOE4, increase monitoring in this population?

The mandatory testing for APOE4 and the subsequent contraindication in APOE4/APOE4 was discussed and was not supported from a safety perspective but also not from an ethical perspective. First, all SAG-N members agreed that the implementation of such a contraindication is not expected to have a substantial effect on the benefit/risk balance. Fatal cases did not occur in the APOE4 homozygous participants, hence, exclusion of these patients will not substantially improve safety profile. The risk of ARIA-E and ARIA-H remain very high in those who are APOE heterozygous (22.7 and 32.4%). Second, it is considered that mandatory testing for APOE genotype will have ethical implications for the patient and their offspring. Another SAG-N expert maintained that, with the slower titration scheme (for which, however, efficacy data are not available), it may be possible to also treat safely homozygotes patients, in which case the genotyping would not be mandatory.

In the view of one patient's representative, mandatory testing for APOE genotype would be acceptable, and he would like to know the risk.

Programme "Early contact with patient organisation"

As part of the programme "Early contact with patient organisation", relevant patient organisations were contacted by EMA. The aim was to enable patients to share their experience, concerns and needs related to their condition and its treatment and healthcare professionals are invited to share to their experience of treating the condition, both of which can be considered early during the assessment process, as appropriate.

Three organisations provided their feedback. The unmet medical in the symptomatic phase (MCI-severe AD) need is particularly underlined by one organisation. Also, a disease modifying mode of action is reported as future treatment in MCI and mild AD. This would require careful patient selection for different therapies which is likely to vary across disease severity as well as aspects of the underlying pathology (such as co-pathology). The amyloid hypothesis is seen as the backbone for AD pathology by one organisation, while acknowledging other processes. Therefore combination therapies with multiple compounds targeting multiple targets are likely needed to achieve this goal. As a consequence, the expectations for a single compound with one target needs to be realistic and although effects on patient related outcomes must be at the absolute forefront, effect sizes needs to be put into context of mode of action of the compound, effects on pathophysiological targets and what is a realistic effect size given the mechanism of action in a progressive disorder. Another point is when to stop treatment in AD and the involvement of patients in treatment approaches and shared decision making. It is also mentioned that patients might be willing to risk potentially serious side effects, even perhaps for relatively modest effect sizes.

The second organisation considers that a long duration of a trial is considered important (>3.5 years) to see relevance on functional endpoints. For medicines intended to slow disease progression in AD, the following topics are considered important: limited efficacy (and lack of clinically relevant endpoints), risk of (serious) side effects (e.g., ARIA, relatively high NNH), high costs, high burden on patient and informal caregivers (many hospital visits, especially burdensome for older people), identification before starting treatment of patients with highest risk of benefit difficult (relatively high NNT).

The third organisation considers that it is very important to stop or delay further deterioration, regardless of a patient's current state (e.g., MCI or mild dementia). The point is not so much about whether a drug is disease modifying, curative or to treat symptoms, but much more about "where you are in your personal journey and how you feel about yourself and your life" (QoL, e.g., manageability of symptoms, coping, fear of progression). This is considered particularly relevant to the issue of

balancing the risks of side effects against the potential benefits. In general, ARIA were perceived as scary and worrying. Some people felt that they would not accept any life-threatening or very serious side effects as their current life was of a very good quality and therefore, it would not be worthwhile to expose themselves to something which could threaten their life. For some people, the more advanced their dementia, the more risk they would be willing to take. Some people felt that progressing to dementia would radically change their life and were ready to accept any side effects, including serious ones. It was expressed that new therapies could also provide indirect benefits, as they would receive more monitoring and follow-up. When discussing meaningful outcome measures, one person explained that the true benefit of a drug lives in being able to "get on and live her life", emphasizing the importance of measures that assess quality of life.

Two organisations mention the Behavioural and Psychological Symptoms of Dementia (BPSD) / neuropsychiatric symptoms as important outcome measure. No outcomes measuring these aspects were included in the pivotal study.

Third party interventions

The CHMP has received interventions from patients' organisations, learned societies and individuals. The interventions – that were duly considered by the Committee – were in support of the approval of donanemab. Points raised in the interventions include:

- the high unmet need for treatments for Alzheimer's Disease;

- the importance of treatments that would delay the progression of symptoms;

- the ability of patients and treating physicians to make informed individual decisions about; treatment;

- the possibility to adequately handle ARIA.

AACI-Long Term Extension Preliminary Results

The Applicant submitted preliminary efficacy and safety data of the long-term extension of the pivotal study AACI very late in the procedure. The main results concern the overall population, including all APOE-E4 genotypes, and not the eventually sought indication of non-carriers only. In addition, analyses seemed to be performed in the EES (details were not provided), and not in the ITT. Moreover, conducted analyses (including assumptions for missing data) are not clearly described. This all immediately limits the interpretation of these data in such a short time window.

3.8. Conclusions

The overall benefit/risk balance of Kisunla is negative.

4. Recommendations

Based on the CHMP review of data on quality, safety and efficacy for Kisunla in the proposed indication 'adult patients with mild cognitive impairment or mild dementia due to Alzheimer's disease (Early Alzheimer's disease) who are apolipoprotein E ε4 (ApoE ε4) non-carriers with confirmed amyloid pathology', and having considered all the available evidence including the responses submitted by the applicant in writing and during Oral Explanations, as well as the outcome of the consultation with the Neurology scientific advisory group, and having considered the magnitude of benefits and risks, and the associated uncertainties, the CHMP considers by majority decision that the efficacy and safety of

the above-mentioned medicinal product are not sufficiently demonstrated, and, therefore, recommends the refusal of the granting of the marketing authorisation for the above-mentioned medicinal product.

The CHMP considers that:

- The magnitude of the effect of Kisunla and the uncertainties of the (long-term) effect beyond a maximum treatment of 18 months do not outweigh the safety concerns.
- Donanemab treatment causes amyloid-related imaging abnormalities (ARIA) in a significant proportion of treated patients, including in the restricted target population proposed. Clinical consequences may be serious and potentially fatal in some patients.

Therefore, it is the opinion of the CHMP that the benefit-risk balance of Kisunla is negative.

The CHMP is of the opinion that pursuant to Article 12 of Regulation (EC) No 726/2004, the safety and efficacy of the above-mentioned medicinal product is not properly or sufficiently demonstrated.

Therefore, the CHMP has recommended the refusal of the granting of the marketing authorisation for Kisunla.

New Active Substance Status

Based on the CHMP review of the available data, the CHMP considers that donanemab is to be qualified as a new active substance in itself as it is not a constituent of a medicinal product previously authorised within the European Union.

5. Re-examination

5.1. Ground #1

"The magnitude of the effect of Kisunla and the uncertainties of the (long-term) effect beyond a maximum treatment of 18 months do not outweigh the safety concerns."

The applicant's response to the CHMP's formal ground#1 for refusal is summarised below and includes copies of the most relevant parts of the detailed applicant's response.

5.1.1. Summary of the ground for re-examination

A disease modifying effect has been demonstrated in the Phase 2 Study AACG and in Phase 3 Study AACI-PC and LTE periods. Supportive efficacy results consistently demonstrated favourable benefit across APOE ε4 subgroups. The results demonstrate statistically significant and clinically meaningful benefit across well-established scales that measure patient's daily activities such as memory, personal care, judgment and problem solving, and community affairs. This includes long-term efficacy data over 3 years in the proposed indicated population of APOE ε4 heterozygotes and noncarriers. The long-term efficacy data became available shortly prior to the initial CHMP Opinion. A preliminary summary was provided at the time. In response to the grounds for the initial negative opinion, the applicant presents placebo-controlled efficacy analyses applying multiple imputation for missing data with copy increments in reference, additional subgroup analyses including the proposed indicated population, sensitivity, and long-term analyses.

Study AACI – Placebo controlled period

Methods

New target population

In the re-examination procedure, the applicant proposes an indication which is different from the target population initially proposed. The applicant now intends to include APOE ε4 heterozygotes and noncarriers (instead of noncarriers only). The efficacy analyses presented for the re-examination procedure therefore aim in providing data which support a positive Benefit/Risk in this specific target population.

The applicant argues that the APOE ε4 heterozygotes and noncarrier population is considered a credible subgroup in line with the key concepts outlined in EMA guideline on subgroups (EMA 2019) based on the following:

- Pre-planned subgroup analyses: The pre-planned subgroup analyses included APOE ε4 genotype for both efficacy (iADRS and CDR-SB) and safety (ARIA incidence).
- Consistency: The efficacy (magnitude of the effect) in the APOE ε4 heterozygotes and noncarrier population is similar to the efficacy in the overall studied population.
- Credibility: Evaluation of clinical response by number of APOE ε4 alleles was prespecified. The efficacy analyses showed consistent results as noted in the consistency bullet above and is feasible to implement in clinical practice (validated tests are available across EU).
- Biological plausibility: In the absence of treatment, APOE ε4 carrier patients have greater incidence of cerebral amyloid angiopathy (Rannikmäe et al. 2013). Across the class of amyloid-targeting therapies, ARIA rates increase with increasing number of APOE ε4 alleles; APOE ε4 heterozygotes are at higher risk of ARIA than noncarrier patients, and APOE ε4 homozygotes have the highest risk (Sperling et al. 2012; Salloway et al. 2022; Honig et al. 2024).
- Replication: The finding of APOE ε4 homozygous genotype as a risk factor for ARIA is replicated in the literature with other medicinal products targeting amyloid (Zimmer et al 2025; Honig et al. 2024). Efficacy in heterozygotes and noncarriers is supported by data published by Sims et al. 2023 and Van Dyck et al. 2023.

Statistical methods

The applicant clarifies that in study AACI-PC pre-specified efficacy analyses were conducted using the evaluable efficacy set (modified ITT population, consisting of participants having both a baseline and at least one follow-up measurement). Missing data were handled as missing at random by the mixed model for repeated measures and the natural cubic spline model. The applicant acknowledges the CHMP request for efficacy analyses to be performed in the ITT population, using MMRM and multiple imputation for missing data.

In the original procedure, the CHMP requested imputation with the 20% lowest change scores for death and ARIA discontinuations and J2R for other reasons as the method for handling

missing data. In the responses to the 2nd List of Outstanding Issues, the applicant submitted a MMRM performed on the change from baseline cognitive scores (iADRS, CDR-SB) using a model that adjusted for the difference in baseline scores among placebo and donanemab groups with and without ARIA-E. At Week 76, least squares mean change scores for participants treated with donanemab with ARIA-E were better than those without ARIA-E (Table 37).

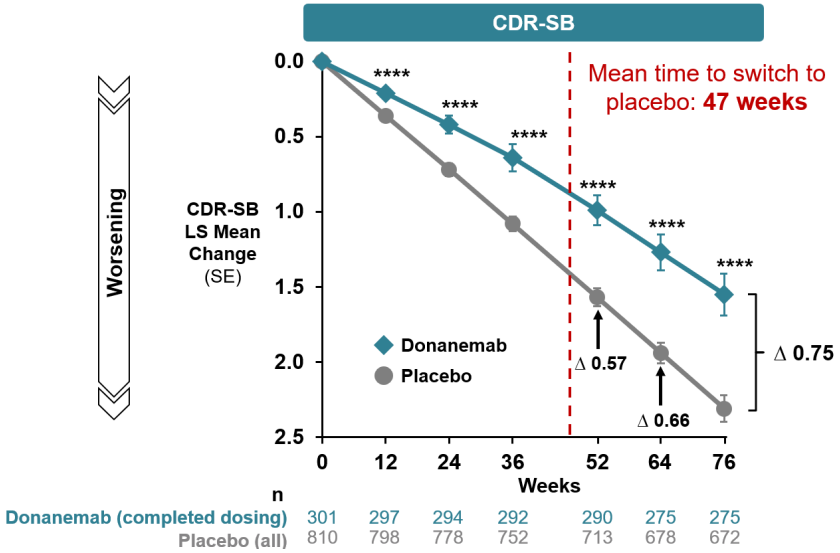
Table 37. MMRM change from baseline by treatment and ARIA-E status overall population, AACI-PC

Clinical Endpoint	Treatment	LS Mean Change Difference at Week 76 (SE)	p-value
iADRS	Dona with ARIA-E	3.928 (1.205)	0.0011
	Dona without ARIA-E	2.749 (0.790)	0.0005
CDR-SB	Dona with ARIA-E	-0.948 (0.211)	<0.0001
	Dona without ARIA-E	-0.627 (0.137)	<0.0001

Abbreviations: AACI = I5T-MC-AACI; ARIA-E = amyloid-related imaging abnormalities – oedema; CDR-SB = Clinical Dementia Rating Scale – Sum of Boxes; Dona = donanemab; iADRS = integrated Alzheimer's Disease Rating Scale; LS = least-squares; MMRM = mixed model for repeated measures; PC = placebo controlled; SE = standard error.

The applicant constitutes that the results show that imputing the lowest 20% of change scores for participants with ARIA-E is overly conservative and does not reflect the impact of donanemab on the patient population.
Following that response, CHMP requested the use of J2R as the method for handling all missing data. After thorough analysis with several different types of reference-based multiple imputation, the applicant proposes the use of CIR to describe the efficacy results as it would yield more realistic estimates than using J2R for a disease modifying treatment.

Figure 18. Efficacy results in participants who switched to placebo after treatment-related amyloid clearance at 6 or 12 months (CDR-SB, Overall Population), Study AACI-PC.



Abbreviations: AACI = I5T-MC-AACI; CDR-SB = Clinical Dementia Rating Scale – Sum of Boxes, LS = least squares, SE = standard error.
Nominal p-values: **** p<0.0001.
Note: The mean time in the clinical trial prior to switch to placebo for these participants was 47 weeks, as shown by the red-dashed vertical line.

The applicant considers, that for that reason, CIR is a more-appropriate approach for imputation of missing data in AACI compared to J2R and is the method the applicant proposes for the efficacy

analyses provided in the grounds for re-examination. This approach will also enable consistency of approaches across the class.

Clinical endpoints in the new target population

iADRS

The iADRS, an integrated assessment of cognition and daily function, comprised of items from the ADAS-Cog13 and ADCS-iADL, was used for the primary endpoint. The applicant points out that the use of an integrated scale like iADRS for assessment in early stages of AD is aligned with EMA guideline on AD (EMA 2018) and that no strict objections to its use were noted in the donanemab Scientific Advice sought in 2021. The applicant also points out that the results on iADRS were supported by the statistically significant and clinically meaningful results of CDR-SB.

CDR-SB

The applicant stresses that the CDR-SB is an established integrated scale that assesses function and cognition and that the robustness of the changes observed were supported by statistically significant changes in established scales measuring cognition on the ADAS-Cog13 and daily function on the ADCS-iADL scale (Figure 6). The applicant also cites the European Alzheimer's Disease Consortium (Jessen et al. 2024) recent position statement article, which states: "the CDR-SB, the iADRS and all other scales used as clinical outcomes measure inherently meaningful features of the disease, namely impairment in cognition and function, which are the core symptoms that define the clinical manifestation of AD".

CDR-SB domains include memory, orientation, judgment, and problem solving, community affairs, home and hobbies, and personal care, which are truly meaningful daily measures experienced by patients with AD and reflected by caregivers.

Results

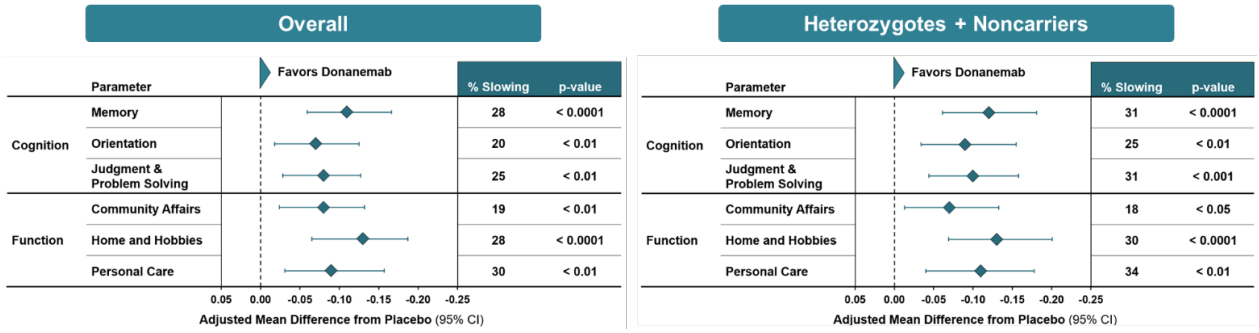
iADRS results in study AACI, week 76

- a 2.44-point difference (95% CI: 1.036 to 3.836; p = 0.0007), representing a 19% slowing in the overall population.
- a 2.70-point difference (95% CI: 1.091 to 4.315; p = 0.0010), representing a 20% slowing in the heterozygotes and noncarrier population

CDR-SB results in study AACI, week 76

- a -0.62-point difference (95% CI: -0.857 to -0.373; p <.0001), representing a 26% slowing in the overall population.
- a -0.70-point difference (95% CI: -0.958 to -0.435; p <.0001), representing a 29% slowing in the heterozygotes and noncarrier population

Figure 19. Clinically relevant treatment effect across CDR-SB domains at 76 weeks



Abbreviation: CI = confidence interval. CIR = copy increments in reference; ITT = Intention-to-Treat; MMRM = Mixed models for repeated measures.
Note: MMRM, ITT population with CIR.

ADAS-Cog13, ADCS-iADL, and MMSE

ADAS-COG13

At Week 76,

• a -1.18-point difference (95% CI: -1.958 to -0.407; p = 0.0028), representing a 17% slowing in the overall population.

• a -1.39-point difference (95% CI: -2.231 to -0.553; p = 0.0012), representing a 20% slowing in the heterozygotes and noncarrier population

ADCS-iADL

At Week 76,

• a 1.37-point difference (95% CI: 0.500 to 2.237; p = 0.0020), representing a 22% slowing in the overall population.

• a 1.48-point difference (95% CI: 0.523 to 2.444; p = 0.0025), representing a 23% slowing in the heterozygotes and noncarrier population

MMSE

At Week 76,

• a 0.38-point difference (95% CI: -0.017 to 0.777; p = 0.0608), representing a 13% slowing in the overall population.

• a 0.41-point difference (95% CI: 0.001 to 0.824; p = 0.0496), representing a 14% slowing in the heterozygotes and noncarrier population

Table 38. MMRM analysis of key clinical endpoints: MI with copy increments in reference for overall population, heterozygotes + noncarriers, and noncarriers in study AACI-PC

	Overall		**Heterozygotes + Noncarriers**		**Noncarriers**	
	Placebo (N = 876)	**Donanemab (N = 860)**	**Placebo (N = 730)**	**Donanemab (N = 717)**	**Placebo (N = 251)**	**Donanemab (N = 259)**
iADRS						
LS mean change (SE) at Week 76	-13.05 (0.516)	-10.62 (0.511)	-13.47 (0.575)	-10.77 (0.578)	-15.84 (1.000)	-12.60 (0.958)
LS Mean Change Difference at Week 76 (SE) [95% CI]	**-**	**2.44 (0.714) [1.036, 3.836]**	**-**	**2.70 (0.821) [1.091, 4.315]**	**-**	**3.24 (1.369) [0.559, 5.930]**
p-value	**-**	**0.0007**	**-**	**0.0010**	**-**	**0.0179**
% Slowing	**-**	**19**	**-**	**20**	**-**	**21**
CDR-SB						
LS mean change (SE) at Week 76	2.39 (0.091)	1.77 (0.091)	2.42 (0.096)	1.72 (0.096)	2.73 (0.187)	2.02 (0.180)
LS mean Change Difference at Week 76 (SE) [95% CI]	**-**	**-0.62 (0.123) [-0.857, -0.373]**	**-**	**-0.70 (0.133) [-0.958, -0.435]**	**-**	**-0.72 (0.255) [-1.218, -0.218]**
p-value	**-**	**<0.0001**	**-**	**<0.0001**		**0.0049**
% Slowing	**-**	**26**		**29**		**26**
ADAS-Cog$_{13}$						
LS Mean Change (SE) at Week 76	6.81 (0.292)	5.63 (0.287)	7.03 (0.308)	5.63 (0.306)	8.35 (0.528)	6.58 (0.512)
LS Mean Change Difference at Week 76 (SE) [95% CI]	**-**	**-1.18 (0.395) [-1.958, -0.407]**	**-**	**-1.39 (0.428) [-2.231, -0.553]**	**-**	**-1.76 (0.751) [-3.238, -0.291]**
p-value	**-**	**0.0028**	**-**	**0.0012**	**-**	**0.0190**
% Slowing	**-**	**17**	**-**	**20**	**-**	**21**
ADCS-iADL						
LS Mean Change (SE) at Week 76	-6.13 (0.321)	-4.77 (0.319)	-6.37 (0.356)	-4.89 (0.343)	-7.64 (0.634)	-5.87 (0.643)
LS Mean change difference at Week 76 (SE) [95% CI]	**-**	**1.37 (0.443) [0.500, 2.237]**	**-**	**1.48 (0.490) [0.523, 2.444]**	**-**	**1.77 (0.915) [-0.028, 3.561]**
p-value	**-**	**0.0020**	**-**	**0.0025**	**-**	**0.0537**
% Slowing	**-**	**22**	**-**	**23**	**-**	**23**
MMSE						

	Overall		Heterozygotes + Noncarriers		Noncarriers	
	Placebo (N = 876)	**Donanemab (N = 860)**	**Placebo (N = 730)**	**Donanemab (N = 717)**	**Placebo (N = 251)**	**Donanemab (N = 259)**
LS Mean Change (SE) at Week 76	-2.98 (0.140)	-2.60 (0.144)	-3.02 (0.151)	-2.60 (0.154)	-3.50 (0.267)	-3.10 (0.268)
LS Mean change difference at Week 76 **(SE) [95% CI]**	**-**	**0.38 (0.202) [-0.017, 0.777]**	**-**	**0.41 (0.210) [0.001, 0.824]**	**-**	**0.41 (0.388) [-0.354, 1.169]**
p-value	**-**	**0.0608**	**-**	**0.0496**	**-**	**0.2943**
% Slowing	**-**	**13**	**-**	**14**	**-**	**12**

Abbreviations: AACI = I5T-MC-AACI; ADAS-Cog$_{13}$ = Alzheimer's Disease Assessment Scale – 13-item Cognitive Subscale; ADCS-iADL = Alzheimer's Disease Cooperative Study – instrumental Activities of Daily Living subscale; CDR-SB = Clinical Dementia Rating Scale – Sum of Boxes; CI = confidence interval; iADRS = integrated Alzheimer's Disease Rating Scale; ITT = intention-to-treat; LS Mean = least-squares mean; MI = multiple imputation; MMRM = Mixed Modes for Repeated Measures; MMSE = mini-mental state examination; N = number of participants at each visit with non-missing values; PC = placebo-controlled; SE = standard error.
Note: MMRM analysis in ITT population

Sensitivity and Supplementary Analyses

Table 39. Change in baseline in iADRS or CDR-SB score at week 76 sensitivity and supplementary analysis, study AACI-PC

Type of Sensitivity or Supplementary Analysis	**Analysis Set**	**Week 76, Dona vs PBO p-Value**
		Overall
iADRS[a]		
Censored data after first occurrence of ARIA-E or IRR	EES	.011
Model included 2 levels for donanemab: with and without ARIA-E during the study	EES, Dona with ARIA-E	<0.001
	EES, Dona without ARIA-E	0.004
Imputed worst response for deaths at all visits following death	EES	0.001
Per-protocol analysis	Per-Protocol Set	<0.001
Completer analysis	Completers Set	<0.001
Multiple imputation with MAR: imputation process included indicators of treatment discontinuation and ARIA occurrence	ITT	<0.0001
Multiple imputation with MNAR: imputed values using CIR method	ITT	0.0007
Multiple imputation with MNAR: imputed values from worst 20% responders for dropouts due to death and ARIA, and imputed values using Jump to Reference method for other missing data	ITT	0.0361
Multiple imputation with MNAR: imputed values as worst observed change for	ITT	0.1869

Type of Sensitivity or Supplementary Analysis	Analysis Set	Week 76, Dona vs PBO p-Value
		Overall
dropouts due to deaths and ARIA, and imputed values using Jump to Reference for other missing data		
CDR-SB[b]		
Model included 2 levels for donanemab: with and without ARIA-E during the study	EES, Dona with ARIA-E	<0.001
	EES, Dona without ARIA-E	<0.001
Multiple imputation with MAR: imputation process included indicators of treatment discontinuation and ARIA occurrence	ITT	<0.0001
Multiple imputation with MNAR: imputed values using CIR method	ITT	<0.0001
Multiple imputation with MNAR: imputed values from lowest 20% responders for dropouts due to death and ARIA, and imputed values using Jump to Reference method for other missing data	ITT	0.0001
Multiple imputation with MNAR: imputed values as worst observed change for dropouts due to deaths and ARIA, and imputed values using Jump to Reference method for other missing data	ITT	0.0091

Abbreviations: AACI = I5T-MC-AACI; ARIA = amyloid-related imaging abnormalities; ARIA-E = amyloid-related imaging abnormalities–oedema/effusions; CDR-SB = Clinical Dementia Rating Scale – Sum of Boxes; CIR = copy increment from reference; Dona = donanemab; EES = evaluable efficacy set; iADRS = integrated Alzheimer's Disease Rating Scale; IRR = infusion-related reaction; ITT = intention to treat; MAR = missing at random assumption; MMRM = Mixed Model Repeated Measures; MNAR = missing not at random assumption; NCS = natural cubic spline; PBO = placebo; PC = placebo controlled.

a NCS2 analysis.
B MMRM analysis.

Tipping Point Analyses

Tipping point analyses were conducted to assess the impact of missing data. After multiple imputation for the ITT population, assuming that data were missing at random, delta values (tipping parameters) were added to the imputed values. Since decreases in iADRS represent decline, negative values were systematically added to the imputed values for donanemab participants while positive values were added to the imputed values for the placebo group. This was done to identify the values at which statistical significance would be lost (i.e. p>0.05).

Increases in CDR-SB represent decline, so positive values were added to the imputed values for donanemab participants, and negative values were added for the placebo group (Table 40).

Table 40. Tipping point values: difference between missing and observed values for each treatment group (delta) to lose statistical significance

	iADRS		CDR-SB	
Population	**Placebo**	**Donanemab**	**Placebo**	**Donanemab**
Overall	1.0	-5.0	-0.25	1.50
Heterozygotes + Noncarriers	0.0	-5.0	-0.50	1.50
Noncarriers	0.0	-2.5	0.00	1.50

Abbreviations: CDR-SB = Clinical Dementia Rating – Sum of Boxes; iADRS = Integrated Alzheimer's Disease Rating Scale.

Key Biomarker Endpoints

At Week 76, donanemab-treated participants had a significant decrease in,

• amyloid centiloid values relative to placebo in heterozygotes and noncarriers ($p<0.0001$), and noncarriers ($p<0.001$) (Table 41)

• plasma p-tau217 relative to placebo in heterozygotes and noncarriers ($p<0.0001$), and noncarriers ($p<0.001$) (Table 42).

Table 41. MMRM analysis of amyloid centiloid change from baseline for overall population, heterozygotes + noncarriers, and noncarriers in study AACI-PC

	Overall		Heterozygotes + Noncarriers		Noncarriers	
	Placebo	**Donanemab**	**Placebo**	**Donanemab**	**Placebo**	**Donanemab**
Amyloid Centiloid						
Mean baseline (SD)	101.75 (34.371)	104.02 (34.417)	102.27 (34.055)	104.20 (34.630)	103.54 (34.45)	104.62 (34.38)
Mean at Week 76 (SD)	101.78 (35.710)	14.95 (22.820)	101.77 (35.685)	12.19 (21.030)	102.81 (36.00)	8.42 (19.43)
LS Mean Change (SE)	-0.67 (0.909)	-87.03 (0.950)	-1.15 (0.987)	-90.40 (1.030)	0.44 (1.66)	-93.59 (1.58)
LS Mean change difference (SE) [95% CI]	**-**	**-86.37 (1.275) [-88.87, -83.87)**		**-89.25 (1.381) [-91.96, -86.54]**	**-**	**-94.04 (2.27) [-98.49, -89.59]**
p-value		**<0.0001**		**<0.0001**	**-**	**<0.001**

Abbreviations: AACI = I5T-MC-AACI; CI = confidence interval; LS Mean = least squares mean; MMRM = Mixed Model for Repeated Measures; N = number of participants in the population; PC = placebo-controlled; SD = standard deviation; SE = standard error.

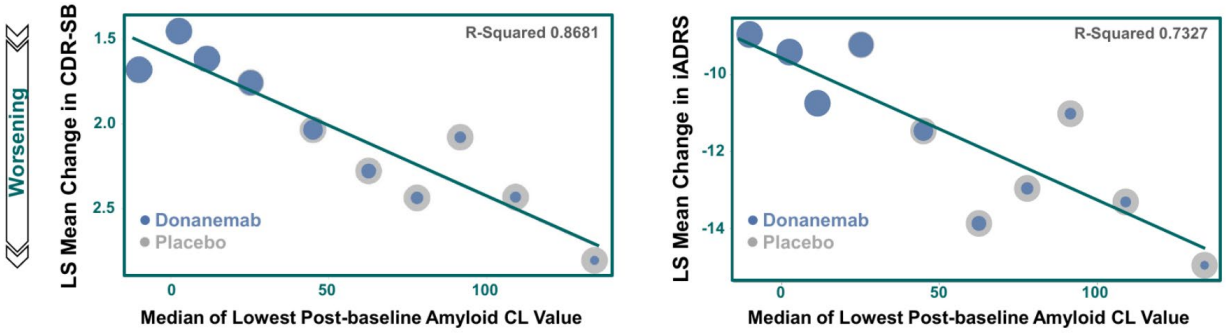
Table 42. MMRM Analysis of plasma P-tau217 (log10) change from baseline for overall population, heterozygotes + noncarriers, and noncarriers in study AACI-PC

	Overall		Heterozygotes + Noncarriers		Noncarriers	
	Placebo	**Donanemab**	**Placebo**	**Donanemab**	**Placebo**	**Donanemab**
Plasma P-tau217						
Mean baseline (SD)	0.66 (0.295)	0.67 (0.304)	0.67 (0.295)	0.68 (0.296)	0.68 (0.28)	0.71 (0.35)
Mean at Week 76 (SD)	0.67 (0.235)	0.46 (0.272)	0.68 (0.242)	0.45 (0.267)	0.69 (0.24)	0.46 (0.29)
LS Mean Change (SE) at Week 76	0.03 (0.008)	-0.19 (0.009)	0.01 (0.009)	-0.22 (0.009)	0.05 (0.01)	-0.21 (0.02)
LS Mean Change Difference at Week 76 (SE) [95% CI]	**-**	**-0.22 (0.012) [-0.24, -0.20]**		**-0.23 (0.013) [-0.26, -0.21]**	**-**	**-0.26 (0.02) [-0.31, -0.22]**
p-value	**-**	**<0.0001**		**<0.0001**	**-**	**<0.001**

Abbreviations: AACI = I5T-MC-AACI; CI = confidence interval; LS Mean = least squares mean; MMRM = Mixed Model for Repeated Measures; N = number of participants in the population; PC = placebo-controlled; P-tau217 = phosphorylated tau at threonine 217; SD = standard deviation; SE = standard error.

A correlation (R-squared = 0.87 and 0.73 for CDR-SB and iADRS, respectively) were observed indicating that patients reaching lower amyloid levels had less disease progression at 18 months (Figure 20).

Figure 20. Correlation between lowest post-baseline amyloid PET and change from baseline in CDR-SB and iADRS: patients reaching lower amyloid levels had less disease progression at 18 months



Abbreviations: CDR-SB = Clinical Dementia Rating – Sum of Boxes; CL = Centiloid; iADRS = integrated Alzheimer's Disease Rating Scale; LS = least square; PET = positron emission tomography.

Responder Analyses

To assess progression to the next stage, patients were evaluated every 3 months for changes during the trial. To be considered progressing to the next stage of disease, a patient had to have 2 consecutive scores greater than their own baseline.

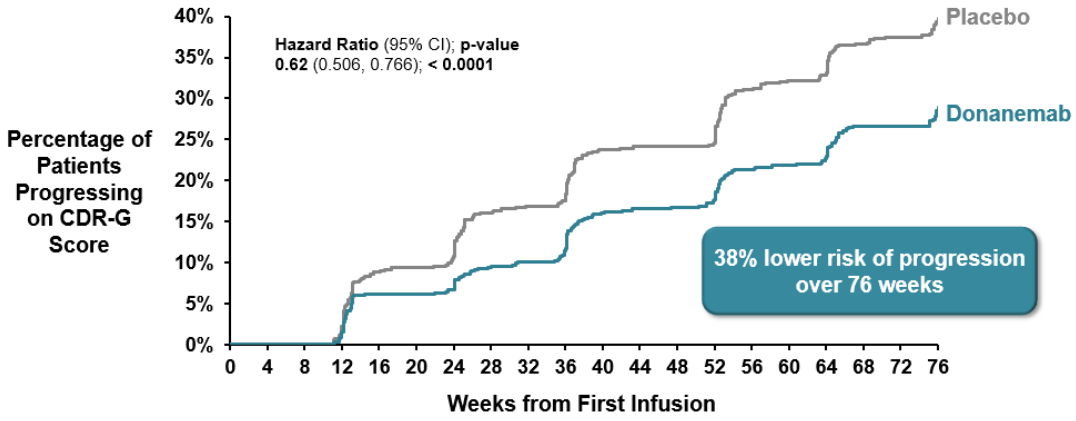
CHMP requested conservative assumptions also included discontinuations due to death and ARIA to be classified as an event.

Significantly more placebo patients worsened to the next stage of the disease compared to donanemab treated patients, representing a

• 34% lower risk of progressing to a worse stage of AD with donanemab treatment in the overall population (HR: 0.66, p<0.0001), and

• 38% lower risk of progressing to a worse stage of AD with donanemab treatment in the heterozygotes and noncarriers (HR:0.62; p<0.0001)

Figure 21. Risk of progression: CDR-G score (Heterozygotes + Noncarriers), Study AACI



Abbreviation: AACI = I5T-MC-AACI; CDR-G = Clinical Dementia Rating –Global; CI = confidence interval

Similar results were obtained using CDR-SB and iADRS for overall population and heterozygotes and noncarriers (Table 43 and Table 44 below). CHMP requested conservative assumptions included discontinuations due to death and ARIA to be classified as an event that met the minimal clinically important difference.

Table 43. CDR analyses of hazard of progressing to next stage in overall population, heterozygotes + noncarriers, and noncarriers

Hazard of Progressing to CDR MCID	Overall Population	Heterozygotes + Noncarriers	Noncarriers
CDR-G			
Any Progression			
HR (95% CI)	0.663 (0.552, 0.797)	0.623 (0.506, 0.766)	0.787 (0.524, 1.182)
p-value	<0.0001	<0.0001	0.2484
% risk reduction	34	38	21
CDR-SB			
≥0.5 point increase			
HR (95% CI)	0.770 (0.676, 0.877)	0.792 (0.684, 0.917)	0.798 (0.592, 1.074)
p-value	<0.0001	0.0018	0.1362
% risk reduction	23	21	20
≥1 point increase			
HR (95% CI)	0.680 (0.591, 0.784)	0.672 (0.572, 0.789)	0.644 (0.466, 0.890)
p-value	<0.0001	<0.0001	0.0077
% risk reduction	32	33	36
≥2 point increase			
HR (95% CI)	0.653 (0.549, 0.777)	0.654 (0.538, 0.797)	0.700 (0.473, 1.035)
p-value	<.0001	<0.0001	0.0736
%risk reduction	35	35	30

Abbreviations: CDR = Clinical Dementia Rating; CDR-G = Clinical Dementia Rating-Global; CDR-SB = Clinical Dementia Rating Scale - Sum of Boxes; CI = confidence interval; HR = hazard ratio; MCID = minimal clinically important difference

Table 44. iADRS analyses of hazard of progressing to next stage in overall population, heterozygotes + noncarriers, and noncarriers

Hazard of Progressing to iADRS MCID	Overall Population	Heterozygotes + Noncarriers	Noncarriers
≥7.5 point decrease			
HR (95% CI)	0.705 (0.598, 0.831)	0.692 (0.576, 0.832)	0.595 (0.409, 0.864)
p-value	<0.0001	<0.0001	0.0064
% risk reduction	30	31	41
≥13.5 point decrease			
HR (95% CI)	0.702 (0.569, 0.866)	0.659 (0.520, 0.835)	0.938 (0.598, 1.470)
p-value	0.0010	0.0005	0.7796
% risk reduction	30	34	6

Abbreviations: CI = confidence interval; HR = hazard ratio; iADRS = integrated Alzheimer's Disease Rating Scale; MCID = minimal clinically important difference

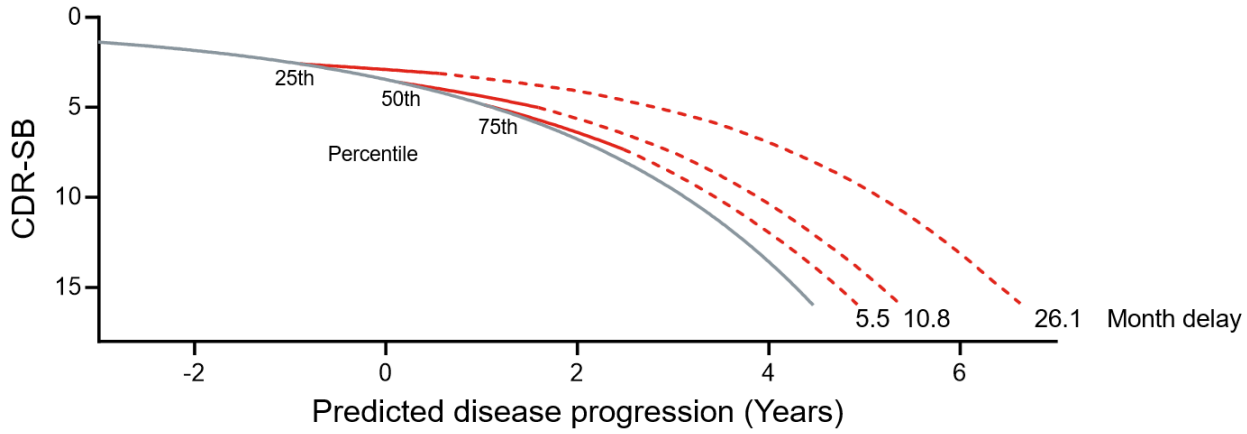
Long-term benefit and delay to severe dementia

In order to estimate disease modifying effects many years after donanemab treatment, a latent-time mixed-effects model was fitted on longitudinal trajectories of CDR-SB scores, staging participants relative to each other on a predicted disease progression time scale. The treatment effect of donanemab during the 76-week AACI-PC period was modelled as proportional time saving (red solid lines), depending on a participant's baseline predicted disease progression. This allows estimation of donanemab efficacy when initiating treatment at different times during the disease course compared to an untreated patient population (grey line).

The estimated effect of treatment initiation by baseline predicted disease progression is illustrated in Figure 9 below. Initiating treatment for patients at the 25th, 50th, or 75th percentiles of the baseline predicted disease progression distribution resulted in a delay of disease progression by 60%, 33%, and 17%, respectively, over the 76-week study period. This analysis is consistent with other prespecified and multiplicity-controlled analyses performed during the 18-month trial which showed a greater percentage of donanemab treated patients earlier in the disease with no clinical change during the first year (Sims et al 2023).

Long-term extrapolation trajectories from a model assuming fading accumulated time savings estimates the delays to severe dementia (estimated time to CDR-SB = 16) as 26.1 months (25th percentile), 10.8 months (50th percentile), and 5.5 months (75 percentile) (Figure 22).

Figure 22. Modelling long-term benefit of donanemab and delay to severe dementia (CDR-SB = 16)



Abbreviations: CDR-SB = Clinical Dementia Rating Scale – Sum of Boxes.

Long-term trajectories of donanemab-mediated delays (red dashed lines) to severe dementia (CDR-SB=16) versus the placebo equivalent predicted disease progression (solid grey line) were extrapolated using a latent-time disease progression model of CDR-SB scores. The estimated effects of treatment initiation at the 25th, 50th, or 75th percentiles of the baseline predicted disease progression distribution are illustrated. This extrapolation scenario corresponds to a fading-slowing scenario where the time savings estimate is updated every 76 weeks since baseline, based on placebo-equivalent predicted disease progression reached after every 76 weeks period.

5.1.2. Assessment of the applicant's responses to the grounds for re-examination (ground #1)

Target population

The target population was restricted to APOE ε4 noncarriers during the initial MAA process. This was in order to address the higher incidence of ARIA in APOE ε4 carriers compared to noncarriers. As part of the re-examination procedure, the applicant is changing its risk minimisation strategy. The new target population will now also include heterozygous carriers. This does not raise objections from the efficacy perspective (see Table 2). With regard to safety, a separate discussion will take place under ground #2.

Effect estimation and meaningfulness

The applicant's position expressed above on handling of missing data is not agreed. The CIR imputation method assumes that after a participant's last observed time point, their missing data will track the changes observed in a specified reference group, such as a placebo arm. This may be plausible for cases in which treatment is discontinued randomly. However, a high amount of missing data is observed after ARIA. It is questionable whether patients who experience symptomatic and serious ARIA would indeed retain the benefit from treatment and thereafter progress as if treated with placebo. Rather, CHMP considers that for these patients, treatment was no longer a viable option and they may have experienced harm that is not properly reflected by CIR.

The applicant's argumentation that at Week 76, least squares mean change scores for participants treated with donanemab with ARIA-E were better than those without ARIA-E does not invalidate our aforementioned objections. This group only includes patients who were able to continue treatment and presumably did not develop severe ARIA symptoms and is therefore not representative for patients with missing data due to more severe ARIA events.

Hence, a more conservative approach, such as J2R seems more appropriate as imputation method – at least for the group of patients which discontinued treatment due to ARIA.

The applicant accepted this objection and submitted additional analyses during the re-examination procedure, based on a different ("hybrid") imputation method. The results of these analyses are provided below (Table 45).

Table 45. Estimation and hypothesis testing using CIR for all missing data versus hybrid approach in APOE ε4 heterozygotes and noncarriers at 18 months

	All Missing Data Handled with CIR	**Requested Hybrid Approach: J2R for Missing Data Due to Death or Severe, Symptomatic, or Serious ARIA Events, and CIR for Other Reasons**
Least squares mean change difference from placebo (% slowing)	donanemab n = 717; placebo n = 730	donanemab n = 717; placebo n = 730
iADRS	2.70 (20%)	2.65 (19.6%)
p-value	0.0010	0.0013
CDR-SB	-0.70 (29%)	-0.69 (28.5%)
p-value	< 0.0001	< 0.0001
ADAS-Cog13	-1.39 (19.8%)	-1.35 (19.3%)
p-value	0.0012	0.0016
ADCS-iADL	1.48 (23.3%)	1.46 (23.0%)
p-value	0.0025	0.0028

Abbreviations: ADAS-Cog13 = Alzheimer's Disease Assessment Scale - 13-item Cognitive (subscale); ADCS-iADL = Alzheimer's Disease Cooperative Study - Instrumental Activities of Daily Living (subscale); APOE ε4 = allele subtype 4 of the gene coding for apolipoprotein class E; ARIA = amyloid-related imaging abnormalities; CDR-SB = Clinical Dementia Rating Scale – Sum of Boxes; CIR = copy increment in reference; iADRS = Integrated Alzheimer's Disease Rating Scale; J2R = Jump to Reference; n = number of participants in the specified category.

In the context of a positive study with adequate type I error control, both clinical efficacy endpoints, iADRS and CDR-SB, are considered adequate to inform on the clinical effectiveness of the Kisunla treatment regimen.

The results indicate a statistically significant treatment effect. This is supported by the results of various sensitivity analyses, all of which confirm a positive treatment effect. However, the magnitude of the treatment effect varies greatly depending on the imputation strategy chosen. With regard to the responder analysis, it should be noted that the CDR-G, as an ordinal scale value from 0 to 3, is a relatively crude instrument for assessing disease progression.

Therefore, some uncertainties still remain regarding the magnitude of the treatment effect.

The applicant presents an extrapolation on the long-term effects of Kisunla treatment, depending on the time point of treatment initiation in relation to disease progression.

Based on the results obtained to date, the assumption that early treatment initiation leads to improved efficacy in terms of time gained until the onset of severe dementia (CDR SB = 16, CDR-G 0 3) appears plausible in principle. However, it is also considered subject to some uncertainty.

CHMP Conclusion on efficacy analyses and results:

The applicant argues that the effect size of efficacy is greater than concluded in the previous CHMP decision. To substantiate this statement, the applicant provides analyses with a different handling of missing data resulting in larger effect estimates.

We assessed these analyses and concluded that

1) assumptions required for the imputation strategy are not plausible for all applicable cases and

2) the benefit-risk balance should not strongly depend on the imputation strategy used.

While there is no reason to question that Kisunla has demonstrated efficacy, for the magnitude of effect still remains some uncertainty because estimates strongly depend on the imputation strategy.

CHMP prefers not to take the risk of overly optimistic assumptions, but considers that the results from a more conservative analysis should be weighed against the risks observed.

In more detail:

After review of several analyses with different imputation strategies it was concluded in the previous assessment (according to the CHMP AR) that "Analyses using MMRM in the ITT population for the primary and all secondary endpoints that use a jump-to-reference imputation method for missing outcomes after ARIA events, death or permanent study discontinuations for other reasons are considered to yield the most realistic estimates".

In the re-examination procedure the applicant argues that these analyses using Jump-to-Reference imputation (J2R) are too conservative and proposes imputation with the Copy-Increment-from-Reference approach (CIR). This approach assumes that from the last existing measurement onwards patients with missing data would experience a decline similar to the control group. This may be plausible for cases in which treatment is discontinued randomly. However, a high amount of missing data is observed after ARIA. It is questionable whether patients who experience symptomatic and serious ARIA would indeed retain the benefit from treatment and thereafter progress as if treated with placebo. Rather, CHMP considers that for these patients, treatment was no longer a viable option and they may have experienced harm that is not properly reflected by CIR.

Efficacy has been demonstrated. In order to characterise the magnitude of the treatment effect even more precisely, the applicant was asked during the re-examination procedure to submit the results with a differentiated approach with regard to the imputation of missing data. A more conservative imputation approach (J2R) was asked to be followed for imputation due to severe/symptomatic ARIA and death. The applicant presented such results (see table above).

5.2. Ground #2

"Donanemab treatment causes amyloid-related imaging abnormalities (ARIA) in a significant proportion of treated patients, including in the restricted target population proposed. Clinical consequences may be serious and potentially fatal in some patients."

The applicant's response to the CHMP's formal Ground#2 for refusal is summarised below. An updated section 4.8 of the SmPC was requested and has been provided regarding the incidences of IRR in the proposed indicated population.

Summary of the ground for re-examination:

ARIA (ARIA-E and ARIA-H) incidence, radiographic severity, symptomatic and serious events, and timing have been well characterised for donanemab in the Phase 3 Study AACI-PC and LTE phase across a 3-year period and in the largest safety database in the class. Consistent with the class, ARIA is a common AE that typically occurs early in treatment. ARIA events were most often mild and asymptomatic and mostly occurred within 6 months of treatment initiation. ARIA events did not cause accelerated deterioration as patients with ARIA had equal or better efficacy results. When symptomatic ARIA occurred, it generally resolved or stabilised upon treatment discontinuation or therapeutic intervention. Serious ARIA was infrequently observed and was rarely fatal. Study AACQ demonstrated that gradual titration of donanemab significantly reduced ARIA-E risk in the overall population and reduced ARIA-E in the indicated populations.

Clear risk-minimisation will:

- exclude APOE ε4 homozygotes from treatment with donanemab,

- include relevant contraindications and warnings outlining the potential risks,
- utilise gradual dose titration,
- use a controlled-access programme to ensure only appropriate patients receive treatment, and
- include targeted MRI monitoring especially early in treatment when most ARIAs occur, along with HCP education and use of a patient card.

Overview on the data package for safety

The development of donanemab as a novel disease modifying treatment option for Alzheimer's disease includes evaluation of safety data collected from over 3500 participants.

ARIA is an important identified risk for donanemab consistent with the class, which rarely presented as symptomatic, serious, or life-threatening without full or partial resolution.

Detailed safety data specific to ARIA and ICH >1 cm are provided from the donanemab clinical programme, in the overall population, proposed indicated population (heterozygotes and noncarriers), and across APOE ε4 genotypes.

Additional analyses include long term safety data from >1200 participants in the proposed indicated population who have been exposed to donanemab over a 36-month period (study AACI-PC and LTE).

Risk factors for ARIA and ICH >1 cm have been identified to inform risk minimisation measures. APOE ε4 homozygous status is a well-established risk factor for ARIA, and the proposed indication is based on exclusion of this group.

Study AACQ

Study AACQ was conducted to evaluate the safety of a modified titration (a gradual up-titration of donanemab) regimen.

PhV and Risk mitigation strategies

Pharmacovigilance activities and risk minimisation measures are proposed and include management of radiographic and symptomatic events as indicated in the proposed label, healthcare professional guide, checklist for prescribers, patient alert card, follow-up questionnaires, and a Controlled Access Programme with restricted distribution. Additionally, two category 1 and one category 3 PAS Studies have been proposed to further characterise ARIA-E, ARIA-H, and ICH greater than 1 cm, as well as the effectiveness of risk minimisation measures and drug utilisation in real world.

Postmarketing data

Up to 9 months of postmarketing data supports the safety profile characterised throughout the donanemab development programme.

Overall safety

The proposed indicated population (APOE ε4 heterozygotes and noncarriers) represent approximately 83% (N = 1447) of the population studied in TRAILBLAZER-ALZ2 (Study AACI).

The safety of donanemab was comprehensively presented in the original submission (SCS) based on data analysed in two analysis sets:

- the **placebo-controlled Dona-PC analysis set** comprised of all participants on donanemab or placebo who received at least 1 dose of study treatment in AACG or in the AACI-PC period (donanemab: N = 984; placebo: N = 999), and
- the **uncontrolled All donanemab analysis set (All-Dona)** comprised of participants who received at least 1 dose of donanemab (N = 2727) in Studies AACG, AACI Main (PC and LTE), AACI A9, AACH Part B and AACN – Dona Cohort.

Overall, results of the integrated safety analysis were found to be consistent with those found in individual donanemab clinical trials and from other amyloid-targeting monoclonal antibody therapies, and did not show an imbalance when compared with placebo other than IRRs and ARIA related events.

An overview of ARIA and ICH >1cm in the All-Dona data set is provided below in Table 46.

Table 46. Overview of ARIA and ICH >1cm; All-Dona analysis set and by APOE ε4 carrier status based on MRI or TEAE cluster

	All Dona (N=2727) n (%)	**Heterozygotes + Non carriers (N=2307) n (%)**	**Noncarriers (N=886) n (%)**	**Heterozygotes (N=1421) n (%)**	**Homozygotes (N=410) n (%)**
Any ARIA-E/-H[a]	825 (30.3)	631 (27.4)	178 (20.1)	453 (31.9)	192 (46.8)
Deaths due to any ARIA/ ICH>1cm[b]	6 (0.2)	6 (0.3)	1 (0.1)	5 (0.4)	0
Any SAE of ARIA	31 (1.1)	18 (0.8)	7 (0.8)	11 (0.8)	12 (2.9)
ARIA-E	531 (19.5)	390 (16.9)	103 (11.6)	287 (20.2)	139 (33.9)
Symptomatic ARIA-E	117 (4.3)	89 (3.9)	28 (3.2)	61 (4.3)	27 (6.6)
SAE ARIA-E	28 (1.0)	16 (0.7)	5 (0.6)	11 (0.8)	11 (2.7)
ARIA-H	699 (25.6)	520 (22.5)	147 (16.6)	373 (26.2)	177 (43.2)
Symptomatic ARIA-H	14 (0.5)	11 (0.5)	3 (0.3)	8 (0.6)	3 (0.7)
SAE ARIA-H	9 (0.3)	3 (0.1)	2 (0.2)	1 (0.1)	6 (1.5)
ICH >1cm	7 (0.3)	7 (0.3)	0	7 (0.5)	2 (0.5)
SAE ICH >1cm	2 (0.1)	3 (0.1)	0	3 (0.2)	0

Abbreviations: AE = adverse event; ARIA = amyloid-related imaging abnormality; ARIA-E = ARIA- oedema/ effusions; ARIA-H = ARIA-haemorrhage/haemosiderin deposition; Dona = donanemab; ICH = intracerebral haemorrhage; MRI = magnetic resonance imaging; N = number of participants; n = number of subjects with at least 1 AE; PC = placebo controlled; SAE = serious adverse event; TEAE = treatment-emergent adverse event.
a Participants may be counted in more than one category.
b Deaths are also included in SAEs and discontinuations due to an AE.

Safety in study AACI-PC

Overview of AEs

- A summary of the overall safety for the proposed population in the AACI-PC analysis set is provided in Table 54.
- In the proposed population, the overall number of deaths included 13 (1.8%) in the donanemab treatment group and 8 (1.1%) in the placebo group. Of the 13 deaths in the donanemab group, a total of 3 participants reported serious ARIA and subsequently died. Further details are provided below.

- A higher frequency of participants reported at least 1 SAE in the donanemab treatment group (17.9%) than in the placebo group (15.2%). The most common SAEs reported in the donanemab group were syncope, ARIA-E, pneumonia, COVID 19, and fall.
- The percentage of participants who discontinued study treatment due to an AE was higher in the donanemab treatment group (12.8%) compared with the placebo treatment group (3.8%), mainly due to ARIA-E, ARIA-H, and infusion-related reactions.
- Overall, the incidence of participants experiencing ≥1 TEAE was higher in the donanemab treatment group (88.9%) compared with the placebo group (81.3%). The most commonly reported events (≥5% and greater than placebo) in the donanemab treatment group were ARIA-E, ARIA-H, fall, headache, IRR, arthralgia, diarrhoea, dizziness, and superficial siderosis of the central nervous system.

Table 47. Overview of safety – overview of adverse events in study AACI-PC

Study AACI-PC	**Overall Population**		**Heterozygotes + Noncarriers**		**Noncarriers**	
	PBO (N = 874) n (%)	Dona (N = 853) n (%)	PBO (N = 728) n (%)	Dona (N = 710) n (%)	PBO (N = 250) n (%)	Dona (N = 255) n (%)
Deaths	10 (1.1)	16 (1.9)	8 (1.1)	13 (1.8)	1 (0.4)	4 (1.6)
Serious AE	138 (15.8)	148 (17.4)	111 (15.2)	127 (17.9)	43 (17.2)	45 (17.6)
Study discontinuation due to AE	32 (3.7)	69 (8.1)	26 (3.6)	54 (7.6)	7 (2.8)	18 (7.1)
Treatment discontinuation due to AE	38 (4.3)	112 (13.1)	28 (3.8)	91 (12.8)	9 (3.6)	28 (11.0)
TEAEs	718 (82.2)	759 (89.0)	592 (81.3)	631 (88.9)	203 (81.2)	212 (83.1)
TEAEs related to study treatment	173 (19.8)	410 (48.1)	133 (18.3)	317 (44.6)	46 (18.4)	95 (37.3)

Abbreviations: AE = adverse event; Dona = donanemab; PBO = placebo; TEAE = treatment emergent adverse event. Participants may be counted in more than one category. Deaths are also included in SAEs and discontinuations due to an AE.

Overview of ARIA and ICH > 1cm in AACI-PC

The applicant provides a side-by-side comparison of ARIA across genotypes and in the proposed indicated population (APOE ε4 heterozygotes and noncarriers) in the AACI-PC analysis set.

Background

While ARIA-E and ARIA-H occur during the natural course of AD, there is an increased risk of both with anti-amyloid antibody treatment (Salloway et al. 2009; Sperling et al. 2011, 2012; Salloway et al. 2014; Carlson et al. 2016; Ketter et al. 2017; Salloway et al. 2022).

ARIA-E is generally transient, reversible, and though it may often be clinically asymptomatic, ARIA can be detected by MRI (Salloway et al. 2009; Ostrowitzki et al. 2012; Sperling et al. 2012; Doody et al. 2014; Salloway et al. 2014, 2022). ARIA can be symptomatic and serious, and fatal in rare cases; therefore, safety monitoring is necessary with amyloid targeting therapies used in slowing disease progression in early symptomatic AD (Zimmer et al. 2025). Of note, symptomatic and severe ARIA events are also relatively higher in frequency in APOE ε4 homozygous carriers (Doran et al. 2024). If symptoms occur, these may include, but are not limited to, headache, confusion, vomiting, unsteadiness, dizziness, tremor, visual disturbances, speech disturbances, worsening cognitive function, alteration of consciousness, and seizures (Ostrowitzki et al. 2012; Sperling et al. 2012; VandeVrede et al. 2020; Mintun et al. 2021; Swanson et al. 2021; Salloway et al. 2022) that may require intervention beyond withholding treatment, such as administration of corticosteroids.

ARIA-H is often associated with ARIA-E, and both are thought to be possibly related to removal of vascular Aβ or amyloid trafficking at the blood-brain barrier (Ketter et al. 2017). Risk factors reported in the literature as being associated with ARIA-H include baseline amyloid load, disease severity (Paczynski M et al 2025) APOE ε4 alleles, preexisting ARIA-H microhaemorrhages (Arrighi et al. 2016, Zimmer et al. 2025), and identification of independent baseline risks for ARIA supports efforts to predict or prevent this adverse event (Zimmer et al. 2025).

Approach to analysis

Although most ARIA-related analyses are based on MRI findings, certain additional analyses have been performed using ARIA AE cluster PTs.

- ARIA-E PT cluster
    - Amyloid-related imaging abnormality-oedema/effusion
    - Brain oedema, and
    - Vasogenic cerebral oedema.
- ARIA-H PT cluster
    - Amyloid-related imaging abnormality-microhaemorrhage and haemosiderin deposits
    - Brain stem microhaemorrhage
    - Cerebellar Microhaemorrhage
    - Cerebral haemosiderin deposit
    - Cerebral microhaemorrhage, and
    - Superficial siderosis of the central nervous system, and
- ICH >1 cm (macrohaemorrhage) PT cluster
    - Cerebral haemorrhage, and
    - Haemorrhagic stroke.

Table 48below provides an overview of ARIA frequency in Study AACI-PC. Table 49 summarises the radiographic severity of ARIA-related events that occurred in Study AACI-PC.

Table 48. Overview of ARIA and ICH>1cm in the overall population, the proposed indicated population[a] and by APOE ε4 genotypes in Study AACI-PC based on MRI or TEAE cluster

Study AACI-PC	**Overall Population**		**Heterozygotes + Noncarriers**		**Noncarriers**		**Heterozygotes**		**Homozygotes**	
	PBO (N = 874) n (%)	**Dona (N = 853) n (%)**	**PBO (N = 728) n (%)**	**Dona (N = 710) n (%)**	**PBO (N = 250) n (%)**	**Dona (N = 255) n (%)**	**PBO (N = 474) n (%)**	**Dona (N =452) n (%)**	**PBO (N =146) n (%)**	**Dona (N =143) n (%)**
Any ARIA (either E or H)	130 (14.9)	314 (36.8)	98 (13.5)	234 (33.0)	30 (12.0)	63 (24.7)	67 (14.1)	170 (37.6)	32 (21.9)	80 (55.9)
Any SAE of ARIA (either E or H)	0	14 (1.6)	0	10 (1.4)	0	2 (0.8)	0	8 (1.8)	0	4 (2.8)
Deaths associated with any ARIA/ ICH>1cm	0	3 (0.4)	0	3 (0.4)	0	1 (0.4)	0	2 (0.4)	0	0
ARIA-E	18 (2.1)	205 (24.0)	13 (1.8)	146 (20.6)	2 (0.8)	40 (15.7)	10 (2.1)	105 (23.2)	5 (3.4)	59 (41.3)
Asymptomatic	18 (2.1)	153 (17.9)	13 (1.8)	106 (14.9)	2 (0.8)	30 (11.8)	10 (2.1)	75 (16.6)	5 (3.4)	47 (32.9)
Symptomatic	0	52 (6.1)	0	40 (5.6)	0	10 (3.9)	0	30 (6.6)	0	12 (8.4)
SAE of ARIA-E	0	13 (1.5)	0	9 (1.3)	0	1 (0.4)	0	8 (1.8)	0	4 (2.8)
Recurrent ARIA-E	0	51 (6.0)	0	35 (4.9)	0	11 (4.3)	0	24 (5.3)	0	16 (11.2)
ARIA-H	119 (13.6)	268 (31.4)	89 (12.2)	196 (27.6)	28 (11.2)	48 (18.8)	61 (12.9)	147 (32.5)	30 (20.5)	72 (50.3)
Asymptomatic	116 (13.3)	258 (30.2)	87 (12.0)	188 (26.5)	27 (10.8)	47 (18.4)	60 (12.7)	140 (31.0)	29 (19.9)	70 (49.0)
Symptomatic	3 (0.3)	10 (1.2)	2 (0.3)	8 (1.1)	1 (0.4)	1 (0.4)	1 (0.2)	7 (1.5)	1 (0.7)	2 (1.4)
Isolated ARIA-H[a]	108 (12.4)	108 (12.7)	84 (11.5)	88(12.4)	28 (11.2)	23 (9.0)	53 (11.2)	64 (14.2)	27 (18.5)	21 (14.7)
Concurrent ARIA-H (with ARIA-E)[ab]	6 (0.7)	137 (16.1)	3 (0.4)	90 (12.7)	0	19 (7.5)	3 (0.6)	70 (15.5)	3 (2.1)	47 (32.9)
SAE of ARIA-H	0	4 (0.5)	0	2 (0.3)	0	1 (0.4)	0	1 (0.2)	0	0
Recurrent ARIA-H	32 (3.7)	108 (12.7)	24 (3.3)	70 (9.9)	7 (2.8)	14 (5.5)	17 (3.6)	56 (12.4)	8 (5.5)	38 (26.6)
ICH>1cm	2 (0.2)	3 (0.4)	2 (0.3)	3 (0.4)	0	0	1 (0.2)	3 (0.7)	0	0
SAE of ICH>1cm	1 (0.1)	1 (0.1)	1 (0.1)	1 (0.1)	0	0	0	1 (0.2)	0	0

Abbreviations: ARIA = amyloid-related imaging abnormality; ARIA-E = ARIA- oedema/effusions; ARIA-H = ARIA-haemorrhage/haemosiderin deposition; Dona = donanemab; ICH = intracerebral haemorrhage; MRI = magnetic resonance imaging; N = number of participants; n = number of subjects with at least 1 AE; PC = placebo controlled; SAE = serious adverse event; TEAE = treatment-emergent adverse event.
a Based on MRI; b Concurrence is defined as ARIA-E and ARIA-H occurring on the same MRI.

Table 49. Overview of ARIA Radiographic severity in the overall population, the proposed indicated population, and by APOE ε4 genotypes, in study AACI-PC

Study AACI-PC	**Overall**		**Heterozygotes + Noncarriers**		**Noncarriers**		**Heterozygotes**		**Homozygotes**	
	PBO (N = 874) n (%)	**Dona (N = 853) n (%)**	**PBO (N = 728) n (%)**	**Dona (N = 710) n (%)**	**PBO (N = 250) n (%)**	**Dona (N = 255) n (%)**	**PBO (N = 474) n (%)**	**Dona (N = 452) n (%)**	**PBO (N = 146) n (%)**	**Dona (N = 143) n (%)**
ARIA-E	17 (1.9)	202 (23.7)	12 (1.6)	144 (20.3)	2 (0.8)	40 (15.7)	9 (1.9)	103 (22.8)	5 (3.4)	58 (40.6)
Mild	13 (1.5)	58 (6.8)	10 (1.4)	44 (6.2)	2 (0.8)	13 (5.1)	8 (1.7)	30 (6.6)	3 (2.1)	14 (9.8)
Moderate	4 (0.5)	130 (15.2)	2 (0.3)	90 (12.7)	0	26 (10.2)	1 (0.2)	64 (14.2)	2 (1.4)	40 (28.0)
Severe	0	14 (1.6)	0	10 (1.4)	0	1 (0.4)	0	9 (2.0)	0	4 (2.8)
Symptomatic,	0	49 (5.7)	0	38 (5.4)	0	10 (3.9)	0	28 (6.2)	0	11 (7.7)
Mild	0	8 (0.9)	0	8 (1.1)	0	3 (1.2)	0	5 (1.1)	0	0
Moderate	0	30 (3.5)	0	22 (3.1)	0	6 (2.4)	0	16 (3.5)	0	8 (5.6)
Severe	0	11 (1.3)	0	8 (1.1)	0	1 (0.4)	0	7 (1.5)	0	3 (2.1)
ARIA-H	115 (13.2)	267 (31.3)	85 (11.7)	195 (27.5)	28 (11.2)	48 (18.8)	57 (12.0)	146 (32.3)	30 (20.5)	72 (50.3)
Mild	92 (10.5)	126 (14.8)	70 (9.6)	102 (14.4)	23 (9.2)	33 (12.9)	47 (9.9)	68 (15.0)	22 (15.1)	24 (16.8)
Moderate	17 (1.9)	52 (6.1)	12 (1.6)	39 (5.5)	3 (1.2)	4 (1.6)	9 (1.9)	35 (7.7)	5 (3.4)	13 (9.1)
Severe	6 (0.7)	89 (10.4)	3 (0.4)	54 (7.6)	2 (0.8)	11 (4.3)	1(0.2)	43 (9.5)	3 (2.1)	35 (24.5)

Abbreviations: ARIA = amyloid-related imaging abnormality; ARIA-E = ARIA- oedema/effusions; ARIA-H = ARIA-haemorrhage/haemosiderin deposition; Dona = donanemab; N = number of participants; n = number of subjects with at least 1 AE; PC = placebo controlled.

ARIA-E (in the proposed indicated population)

Frequency

The incidence of ARIA-E in donanemab treated-participants was higher in the overall population (24%) than the proposed indicated population (20.6%).

Radiographic Severity

The severity of ARIA-E identified on centrally read MRIs was defined using the 3- and 5-point ARIA-E severity scales provided in the study by Bracoud et al. (2017).

If a participant experienced multiple ARIA-E events, the event with the worst severity was stated.

144 participants (20.3%) had ARIA-E based on MRI. Of these, approximately 93% of cases were mild to moderate in severity. 1.4% had severe ARIA-E.

Symptomatic ARIA-E

When ARIA-E was identified on centrally read MRIs, the investigator was to complete the ARIA case report form regarding the presence or absence of symptoms related to the ARIA-E:

- 40 (5.6%) donanemab-treated participants had symptomatic ARIA-E
- 106 (14.9%) donanemab-treated participants had asymptomatic ARIA-E (based on MRI or TEAE cluster).

Symptomatic ARIA E was mild to moderate in severity in >75% cases, and its frequency was higher in carriers versus noncarriers. The most commonly reported symptoms included headache, confusional state, dizziness, nausea, and seizure. Reference is made to Table AACI.8.184 of the AACI CSR (by-patient listing of patients with clinical symptoms associated with ARIA-E).

Serious ARIA-E including deaths

Serious ARIA-E was reported in 9 (1.3%) donanemab-treated patients compared with none in placebo-treated patients, while all of them were symptomatic. The frequency of serious ARIA-E was higher in donanemab-treated APOE ε4 carriers versus noncarriers.

Two participants with serious ARIA-E had **fatal outcomes**.

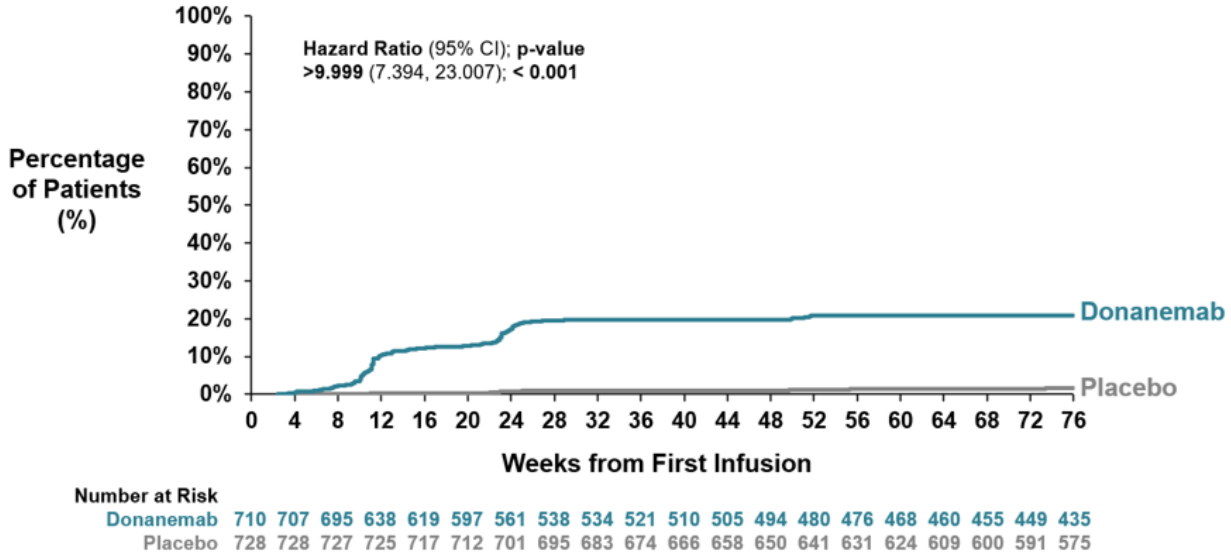
- a 70-80-year-old with APOE genotype ε3/ε4 and intermediate baseline tau. Screening MRI was normal. The last dose (3rd 700-mg dose) of the study drug prior to the SAE of ARIA-E was on Day 56. On Day 66, the participant presented with symptoms of being extremely confused, agitation, forgot to complete tasks, short attention span, garbled speech at times, and disorientation, and an SAE of ARIA-E (severe) was reported. A CT angiograph without contrast showed a potential subacute right-sided stroke and multifocal areas of vasogenic oedema in the right cerebral hemisphere. Epileptic activity was deemed possible because the patient's language was disrupted. On Day 72, head CT scan was suspicious for new foci of subarachnoid haemorrhage; extensive vasogenic oedema remained stable. On Day 75, the participant was discharged to hospice and died on Day 80. Death resulted in permanent discontinuation from study drug and was rated as related to donanemab.
- A 70-80-year-old with APOE genotype ε3/ε4 with intermediate baseline tau. On Day 79, after 3 doses of donanemab 700 mg, the patient's MRI scan showed presence of severe ARIA-E in the right frontal, occipital, parietal, and temporal lobes (initial identification) and presence of 11 microhaemorrhages. The participant was reported with severe ARIA-E and mild ARIA-H. No symptoms were reported. Study drug was interrupted due to ARIA-E and ARIA-H. On Day 167, the event of ARIA-H was considered resolved. On Day 202, study drug was restarted after complete resolution of ARIA-E. On Day 413, a symptomatic AE of ARIA-E (severe) was

reported. The last dose (10th dose) of donanemab prior to this AE of ARIA-E was on Day 399. In total, the participant had received 7 doses of 700 mg and 3 doses of 1400 mg. The patient experienced confusional state and balance disorder, both of moderate severity. On Day 427, the participant was hospitalised due to the SAEs of ARIA-E and ARIA-H. On the same day, the participant experienced nausea and vomiting (moderate severity). Corrective treatment with dexamethasone was initiated. On Day 428, the participant was discharged from hospital and transferred to inpatient hospice and died on Day 447. No autopsy was performed. The last dose of study drug received was on Day 399. The death was rated as related to study drug.

Onset/ Resolution of ARIA-E

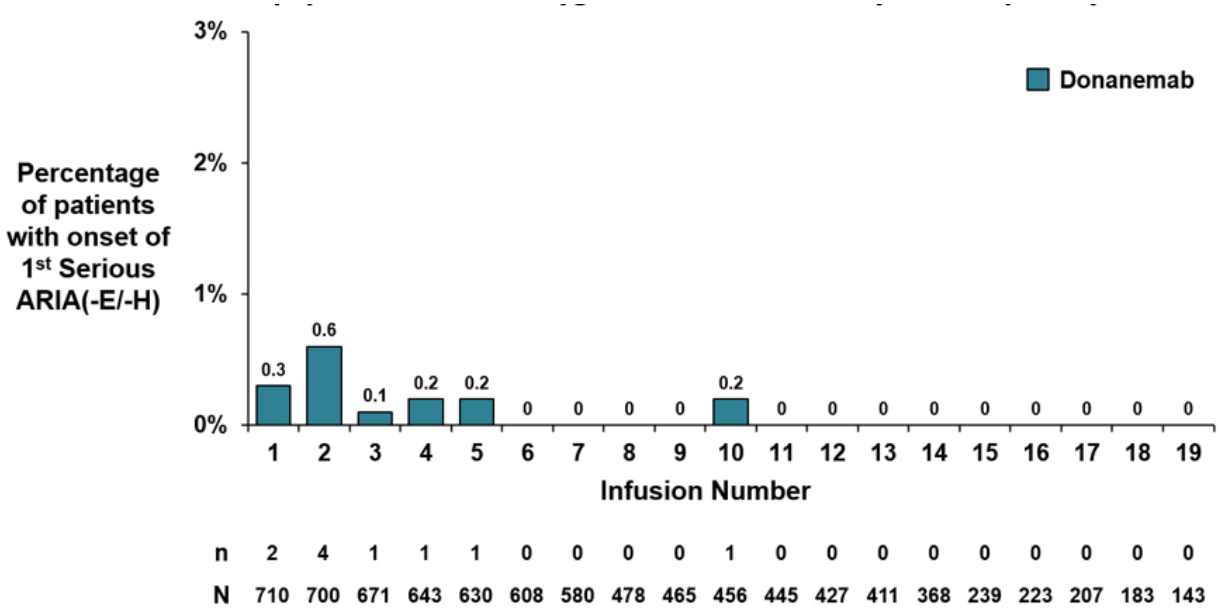
Most ARIA-E events in donanemab-treated participants were first observed within 24 weeks of treatment initiation and most (~63%) participants with serious ARIA-E experienced the ARIA event by the 12th week of treatment. No significant difference in time to onset of ARIA-E by genotype was observed (Figures 23 and 24).

Figure 23. Kaplan-Meier curve for time to first ARIA-E for population of heterozygotes and noncarriers based on MRI or TEAE cluster safety report (AACI-PC period)



Abbreviations: AACI = I5T-MC-AACI; ARIA-E = Amyloid-related imaging abnormalities-oedema/effusion; CI = confidence interval; MRI = magnetic resonance imaging; PC = placebo controlled; TEAE = treatment emergent adverse event

Figure 24. Histogram of serious ARIA (-E/-H) events based on TEAE cluster by donanemab infusion number for population of heterozygotes and noncarriers (AACI-PC period)



Abbreviations: AACI = I5T-MC-AACI; n = number of subjects with onset of first Serious ARIA (-E/-H) event after the specified infusion and prior to or on the same day as any following infusions; MRI = magnetic resonance imaging; N = number of subjects observed at the specified Donanemab infusion number; LY = LY3002813; PC = placebo controlled; TEAE = treatment emergent adverse event.

Based on MRI, the majority of first ARIA-E episodes had complete resolution, with a median time of 58.0 days (mean time of 72.4 days). The majority of donanemab-treated participants who experienced symptomatic ARIA-E had resolution of symptoms during the study. At the time of data lock in Study AACI-PC, a low number (8 of 52) of participants had unresolved symptoms:

- Three of these participants died due or subsequent to ARIA.
- Four of the remaining 5 participants discontinued the study, 3 of these 4 participants had a serious ARIA-E event that led to discontinuation.
- One of the 4 had a non-serious event of ARIA-E and discontinued due to participant decision
- One of the 8 participants who continued in the study reported the resolution of symptoms (diplopia and balance disorder) later after the data cut-off.

Additional review of the cases suggests information on symptom resolution was either not available due to participant discontinuation from the study, or the ongoing symptoms were confounded by underlying disease symptoms, or due to the ARIA event being fatal. There appears to be no conclusive evidence that the unresolved symptoms are long-term sequelae of ARIA-E, and no frequency or pattern of unresolved symptoms is observed to inform on the clinical implications.

Recurrence of ARIA-E

The majority (>75%) of participants with ARIA-E experienced a single episode. Approximately 4.9% of donanemab-treated participants experienced ≥2 episodes of ARIA-E; during the AACI-PC period.

ARIA-H (in the proposed indicated population)

Frequency

ARIA-H occurred more frequently in donanemab-treated participants (based on MRI or TEAE cluster) compared with placebo (27.6% vs. 12.2%), although the frequency of isolated ARIA-H, reflective of haemorrhagic events occurring in the absence of ATT exposure in patients with Alzheimer's Disease, was similar for placebo (11.5%) and donanemab (12.4%).

Concurrent ARIA-E and ARIA-H were observed in 90 (12.7%) of donanemab treated participants compared with 3 (0.4%) of placebo treated participants.

The incidence of ARIA-H (including isolated ARIA-H and concurrent ARIA-E/H) was higher in donanemab treated-participants in the overall population (31.4%) than the proposed indicated population (27.6%).

Radiographic Severity

195 participants (27.5%) had ARIA-H based on MRI. Of these, ~ 72% of cases were mild to moderate in severity, 7.6% had severe ARIA-H.

Symptomatic ARIA-H

- 8 (1.1%) of donanemab-treated participants had symptomatic ARIA-H
- 188 (26.5%) of donanemab-treated participants had asymptomatic ARIA-H

The frequency of symptomatic ARIA-H was higher in carriers versus noncarriers.

Serious ARIA-H including deaths

Serious ARIA-H was reported in 2 (0.3%) donanemab treated participants.

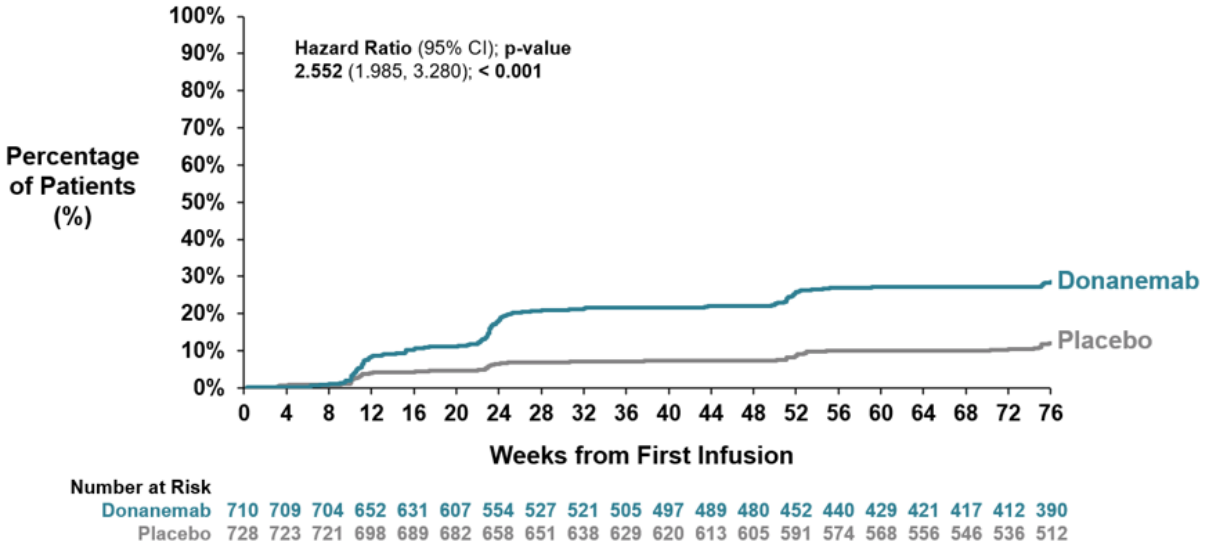
Both participants with SAEs of ARIA-H subsequently died, one of whom also had concurrent serious ARIA-E and is described in the above section on ARIA-E).

- A 70-to-80-year-old noncarrier of APOE4 with intermediate baseline tau. The participant's screening MRI scan showed SS in the left frontal lobe. On Day 46, the participant had a TEAE of mild symptomatic ARIA-E with mild right frontotemporal headache. Treatment was temporarily interrupted due to ARIA-E and not restarted. On Day 71, the participant's MRI scan showed presence of mild+ ARIA-E in left parietal, right occipital, and right temporal lobes; presence of 1 microhaemorrhage, SS in the left frontal, right occipital, right parietal, and right temporal lobes. On Day 72, an SAE of severe ARIA-H was reported. The participant experienced unstable gait on the right side and was hospitalised due to hemiplegia and aphasia, with severe cerebral haemorrhage and haemorrhagic stroke with mass effect. A head CT scan showed presence of a large haematoma in the left posterior parietal region. The participant's condition deteriorated, and he was transferred to palliative care. On Day 75, the study participant died. An autopsy was not performed. The cause of death was reported as haemorrhagic stroke and ARIA-H. The TEAE of ARIA-E and the SAE of ARIA-H were rated as related to donanemab.

Onset of ARIA-H

Most ARIA-H events in donanemab-treated participants were first observed within 24 weeks of initiation of events (Figure 25). No difference in time to onset of ARIA-H was observed between genotypes (Figure APP.6.6, Figure APP.6.7, Figure APP.6.8).

Figure 25. Kaplan-Meier curve for time to first ARIA-H for population of heterozygotes and noncarriers based on MRI or TEAE cluster (AACI-PC period)



Abbreviations: AACI = I5T-MC-AACI; CI = confidence interval; ARIA-H = amyloid-related imaging abnormality–haemorrhage or haemosiderin deposition; MRI = magnetic resonance imaging; PC = placebo controlled; TEAE = treatment emergent adverse event.

Recurrence of ARIA-H

The majority of participants with ARIA-H experienced a single episode of ARIA-H. ~ 9.9% of donanemab-treated participants experienced >1 episode of ARIA-H during the AACI-PC period.

ICH > 1 cm (in the proposed indicated population)

Frequency

A total of 3 (0.4%) donanemab-treated participants and 2 (0.3) placebo-treated participants reported ICH >1cm.

Serious ICH > 1cm including death

One participant from each treatment group reported 1 serious ICH > 1cm event.

Although, there were no ICH related fatalities reported in either treatment arm in Study AACI-PC, as previously described in the initial SCS, a fatal thalamic haemorrhage was reported in Study AACI -A9:

A 70-to-80-year-old (APOE ε4 heterozygote) with hypertension, insulin-requiring type 2 diabetes mellitus, hyperlipidaemia, Parkinsonism, and stroke fulfilled the dose-stopping criteria after receiving his 14th dose of donanemab on Day 370. The most recent brain MRI on Day 364 did not show ARIA. On Day 409, the patient had a thalamic haemorrhage and died on Day 421.The cause of death was reported as thalamic haemorrhage. According to assessment, it was most likely hypertensive haemorrhage. The patient was off study drug at the time of the event, which was rated as related to donanemab.

Post-treatment safety

Since treatment with donanemab can be stopped following amyloid plaque clearance, safety in participants after treatment discontinuation/ completion has been followed. A response was previously submitted as part of the Day 180 List of Questions (Q 27). Overall, the safety profile of donanemab-treated participants post-treatment is similar to that observed with placebo-treated participants in

Study AACI-PC. Overall, a higher frequency of ARIA-E or -H events has been observed in the group with a previous ARIA event.

Since the proposed indicated population excludes APOE ε4 homozygotes, the post treatment safety as regards ARIA events would be further improved. However, a cautionary statement is proposed in Section 4.4 of the SmPC for ARIA in high-risk patients irrespective of treatment.

Analysis of the post-treatment population included participants from Study AACI-PC who received donanemab during the placebo-controlled period and were no longer receiving donanemab in the post-treatment period, as they

- discontinued treatment but remained in the follow-up period
- discontinued treatment but remained in the study, or
- switched to placebo due to amyloid clearance.

Of note, this analysis was done for the overall population in study AACI-PC, which included APOE ε4 carriers with a data cut-off of 30 August 2024.

Baseline of post-treatment for the analyses was defined as the last dose plus 57 days of donanemab treatment and data until end of the follow-up period or data cut-off were evaluated. Post-treatment safety data were evaluated from a total of 657 donanemab-treated participants. These included 256 participants who had experienced any ARIA event and 401 participants without an ARIA event during their exposure to donanemab. The median duration of the post treatment follow-up period was 573 days (403 days for those with an ARIA event and 651 days for those with no ARIA event during donanemab exposure). Overall, death was reported in approximately 2% of the participants after discontinuation of donanemab treatment (Table 50) that were numerically higher in those without ARIA during their exposure to donanemab. None of the deaths were ARIA or ICH related. The frequencies of SAEs and discontinuation of study and treatment due to an AE were comparable to the frequency observed in participants treated with placebo in Study AACI-PC.

Table 50. Overview of adverse events, Study I5T-MC-AACI (post-treatment); data cut-off = 30 August 2024

	AACI-PC Post-treatment			**AACI-PC**
	ARIA during Dona	**No ARIA during Dona**	**Total**	
	Donanemab (N = 256) n (%)	**Donanemab (N = 401) n (%)**	**Donanemab (N = 657) n (%)**	**Placebo (N = 874) n (%)**
Deaths	4 (1.6)	11 (2.7)	15 (2.3)	10 (1.1)
SAEs	36 (14.1)	73(18.2)	109 (16.6)	138 (15.8)
Discontinuation from study due to an AE	9(3.5)	14 (3.5)	23 (3.5)	32 (3.7)
Discontinuation from study treatment due to an AE	9 (3.5)	15 (3.7)	24 (3.7)	38 (4.3)
TEAEs	174 (68.0)	280 (69.8)	454 (69.1)	718 (82.2)

Abbreviations: AACI = I5T-MC-AACI; AE = adverse event; ARIA = amyloid-related imaging abnormalities; Dona = donanemab; n = number of participants with at least 1 AE; N = number of participants; PC = placebo controlled; SAE = serious adverse event; TEAE = treatment-emergent adverse event.

ARIA

Table 51 provides an overall summary of ARIA events observed in donanemab-treated participants post-treatment. The increased frequency of overall ARIA events in the post-treatment group compared with placebo during the AACI-PC period was primarily driven by ARIA-H events, which are known to

occur naturally, to some extent, in the AD population. Frequencies of both ARIA-E and ARIA-H post-treatment were higher in those with a prior ARIA event during donanemab treatment compared with those without an ARIA event. Participants with a prior ARIA event represent a subgroup with higher frequency of APOE ε4 carriers and other baseline MRI risk factors compared to the population without a prior ARIA event as observed in analysis of ARIA events during donanemab treatment. By contrast, the subgroup with no prior ARIA event is enriched for noncarriers and shows a lower frequency of ARIA events (both ARIA-E and ARIA-H) compared with the placebo participants that represent a mix population of carriers and noncarriers. Additionally, while the frequency and incidence rates of ARIA-E or ARIA-H post-treatment appear relatively higher than those observed in placebo-treated participants in Study AACI-PC, it is important to note that the overall number of participants and the observation times in this subgroup of participants is much lower.

Moreover, participants with ARIA events in the treatment period may have more frequent MRIs post treatment to monitor for resolution of ARIA-E and stabilisation of ARIA-H that maybe continuing from the treatment period, resulting in greater identification of post-treatment-emergent asymptomatic ARIA, especially ARIA-H events.

Table 51. Summary of ARIA events, study I5T-MC-AACI (post-treatment); data cut-off = 30 August 2024

	AACI-PC Post-treatment			**AACI-PC**
	ARIA during Dona	**No ARIA during Dona**	**Total**	
	Donanemab (N = 256) PYO = 290.8 n (%) [OAIR]	**Donanemab (N = 401) PYO = 545.3 n (%) [OAIR]**	**Donanemab (N = 657) PYO = 836.1 n (%) [OAIR]**	**Placebo (N = 874) PYO = 1238.9 n (%) [OAIR]**
ARIA[a] total events	73 (28.5) [32.4]	46 (11.5) [9.3]	119(18.1) [16.5]	130 (14.9) [11.5]
ARIA-E[a]	9 (3.5) [3.2]	6 (1.5) [1.1]	15 (2.3) [1.8]	18 (2.1) [1.5]
SAE	0	0	0	0 (0.0) [0.0]
Symptomatic[a,b]	0	1 (0.2) [0.2]	1 (0.2) [0.1]	1 (0.1) [0.1]
ARIA-H[a]	70 (27.3) [30.7]	42 (10.5) [8.4]	112 (17.0) [15.4]	119 (13.6) [10.4]
SAE	0	0	0	0 (0.0) [0.0]
Symptomatic[a,b]	0	1 (0.2) [0.2]	1 (0.2) [0.1]	3 (0.3) [0.2]
Intracerebral haemorrhage greater than 1 cm[c]	0	0	0	2 (0.2) [0.2]

Abbreviations: AE = adverse event; ARIA = amyloid-related imaging abnormalities; ARIA-E = amyloid-related imaging abnormalities-oedema; ARIA-H = amyloid-related imaging abnormalities-haemorrhagic; CRF = case report form; Dona = donanemab; MRI = magnetic resonance imaging; n = number of participants with at least 1 AE; N = number of participants; OAIR = incidence rates adjusted for observation time; PC = placebo controlled; PYO = patient-years of observation time; SAE = serious adverse event; TEAE = treatment-emergent adverse event.

a Based on MRI or TEAE cluster output.

b Based on ARIA CRF for ARIA-E or AE reporting for ARIA-H.

c Based on TEAE cluster including cerebral haemorrhage and haemorrhagic stroke.

Safety in study AACI-LTE

Study AACI included a blinded extension period (18 months) making the entire study duration of up to 36 months. Data from the extension were submitted at a late stage of the first evaluation procedure.

This response provides further analyses and tabulations for the proposed indicated population over the 36-month period.

A total of 1510 participants received donanemab either during the placebo period (early start group, N=853) or starting donanemab in the LTE period (delayed start group, N=657; previously randomised to placebo) in Study AACI. Of these 1207 (delayed start group N=657 plus participants from early start N=550) continued in the LTE period. Overall,

- Safety observations were consistent between the early and delayed start groups.
- In the LTE period, frequencies of adverse events of special interest did not increase for early start donanemab participants.
-

No new safety signals were observed compared to the established safety profile.

Table 52. Overview of adverse events

Participants[a]	**PC: Placebo (N=874) n (%)**	**PC: Donanemab (N=853) n (%)**	**LTE: Randomised to Placebo in PC Period (N=657) n (%)**	**LTE: Randomised to Donanemab in PC Period (N=550) n (%)**
Deaths[b]	11 (1.3)	17 (2.0)	7 (1.1)	10 (1.8)
Serious AE	130 (14.9)	148 (17.4)	129 (19.6)	101 (18.4)
Study discontin. due to AE	37 (4.2)	73 (8.6)	39 (5.9)	21 (3.8)
Treatment discontin. due to AE	41 (4.7)	115 (13.5)	89 (13.5)	21 (3.8)
TEAEs	722 (82.6)	763 (89.4)	568 (86.5)	448 (81.5)
TEAEs related to study treatment[c]	176 (20.1)	414 (48.5)	315 (47.9)	101 (18.4)

Abbreviations: AE = adverse event; LTE = long-term extension; N = number of subjects with at least one adverse event during any time period; PC = placebo-controlled; SAE = serious adverse event; TEAE = treatment-emergent adverse event.

[a] Participants may be counted in more than one category.
[b] Deaths are also included as SAEs and discontinuations due to AEs
[c] Includes events that were considered related to study treatment as judged by the investigator.

Overview of AEs in AACI-LTE

Safety observations for donanemab during the LTE period were similar to those observed in the PC period. A total of 1247 participants from the proposed indicated population of APOE ε4 heterozygotes and noncarriers received donanemab either during the placebo period (early start N=710) or started donanemab in the LTE period (delayed start N=537; previously randomised to placebo) in study AACI. Of these, 1002 (delayed start group N=537 plus participants from early start N=465) continued in the LTE study period. Participants from the delayed start group had similar frequencies of SAEs, and TEAEs to those in the early start group despite being older and more clinically advanced. The aged and advanced target population may have resulted in higher treatment discontinuations due to adverse events.

Table 53 below compiles safety results for Study AACI-PC and AACI-LTE for all donanemab treated participants in the overall population and the proposed indicated population, including observation time adjusted incidence rates.

- Two deaths related to ARIA/haemorrhage occurred in the delayed start group. One participant (APOE ε4 heterozygote) had a fatal ARIA-E and the other participant (APOE ε4 heterozygote) had a fatal intracranial haemorrhage following treatment with a thrombolytic agent in presence of ARIA-E.

Table 53. Overview of safety - overview of adverse events in study AACI-PC and LTE

Study AACI-PC LTE	**Overall Pop[a] (N = 1510) (PYO=2949.1) n (%) [OAIR]**	**Heterozygotes + Noncarriers[a] (N = 1247) n (%) (PYO = 2451.3) [OAIR]**	**Noncarriers[a] (N = 440) (PYO = 866.5) n (%) [OAIR]**
Deaths	35 (2.3) [1.2]	30 (2.4) [1.2]	13 (3.0) [1.5]
Serious AE	360 (23.8) [13.7]	304 (24.4) [14.0]	118 (26.8) [15.4]
Study discontinuations due to AE	134 (8.9) [4.6]	102 (8.2) [4.2]	39 (8.9) [4.6]
Treatment discontinuations due to AE	226 (15.0) [8.1]	172 (13.8) [7.4]	65 (14.8) [7.9]
TEAEs	1372 (90.9) [201.9]	1131 (90.7) [196.6]	390 (88.6) [173.4]
TEAEs related to study treatment	777 (51.5) [43.6]	597 (47.9) [38.3]	177 (40.2) [30.0]

Abbreviations: AACI = I5T-MC-AACI; AE = adverse event; LTE = long term extension; N = number of participants; PC = placebo controlled; SAE = serious adverse event; TEAE = treatment-emergent adverse event.

a All participants in the specified population who have received donanemab during PC and/or LTE Period.

Overview of ARIA and ICH > 1cm in AACI-LTE

Table 54 and Table 55 below provide an overview of ARIA events and ICH > 1cm in the overall, proposed indicated population of APOE ε4 heterozygotes and noncarriers and by APOE ε4 genotypes in all donanemab treated participants during study AACI-PC and LTE periods.

Table 54. Overview of ARIA and ICH>1cm in overall population, all APOE ε4 Genotypes, and proposed indicated population in study AACI-PC and AACI-LTE based on MRI or TEAE cluster

Study AACI-PC and AACI-LTE	**Overall** (N = 1510) n (%)	**Heterozygotes + Noncarriers** (N = 1247) n (%)	**Noncarriers** (N = 440) n (%)	**Heterozygotes** (N = 804) n (%)	**Homozygotes** (N = 263) n (%)
Any ARIA (either E or H)	655 (43.4)	487 (39.1)	130 (29.5)	356 (44.3)	168 (63.9)
Any SAE of ARIA (either E or H)	24 (1.6)	17 (1.4)	4 (0.9)	13 (1.6)	7 (2.7)
Deaths associated with any ARIA/ICH>1cm	5 (0.33)	5 (0.4)	1 (0.23)	4 (0.5)	0
ARIA-E	384 (25.4)	269 (21.6)	74 (16.8)	194 (24.1)	115 (43.7)
Asymptomatic	288 (19.1)	198 (15.9)	53 (12.0)	144 (17.9)	90 (34.2)
Symptomatic	96 (6.4)	71 (5.7)	21 (4.8)	50 (6.2)	25 (9.5)
SAE of ARIA-E	23 (1.5)	16 (1.3)	3 (0.7)	13 (1.6)	7 (2.7)
Recurrent ARIA-E	93 (6.2)	61 (4.9)	20 (4.5)	41 (5.1)	2 (12.2)
ARIA-H	579 (38.3)	427 (34.2)	108 (24.5)	318 (39.6)	152 (57.8)
Asymptomatic	565 (37.4)	416 (33.4)	106 (24.1)	309 (38.4)	149 (56.7)
Symptomatic	14 (0.9)	11 (0.9)	2 (0.5)	9 (1.1)	3 (1.1)
Isolated ARIA-H[a]	269 (17.8)	216 (17.3%)	55 (12.5)	161 (20.0)	53 (20.2)
Concurrent ARIA-H (with ARIA-E)[a,b]	270 (17.9)	179 (14.4%)	42 (9.5)	136 (16.9)	91 (34.6)
SAE of ARIA-H	4 (0.3)	2 (0.2)	1 (0.2)	1 (0.1)	2 (0.8)
Recurrent ARIA-H	243 (16.1)	163 (13.1)	39 (8.9)	124 (15.4)	80 (30.4)
ICH > 1cm	10 (0.7)	7 (0.6)	1 (0.2)	6 (0.7)	3 (1.1)
SAE of ICH > 1cm	2 (0.1)	2 (0.2)	1 (0.2)	1 (0.1)	0 (0.0)

Abbreviations: AACI = I5T-MC-AACI; ARIA = amyloid-related imaging abnormality; ARIA-E = ARIA- oedema/effusions; ARIA-H = ARIA-haemorrhage/haemosiderin deposition;
LTE = long term extension; ICH = intracerebral haemorrhage; MRI = magnetic resonance imaging; N = number of participants; n = number of subjects with at least 1 AE; PC = placebo controlled; SAE = serious adverse event; TEAE = treatment-emergent adverse event.

a Based on MRI

b Concurrence is defined as ARIA-E and ARIA-H occurring on the same MRI

Table 55. Overview of ARIA radiographic severity in overall population, all APOE ε4 genotypes, and proposed indicated population study AACI-PC and AACI-LTE based on MRI

Study AACI-PC LTE	**Overall** (N = 1510)	**Heterozygotes + Noncarriers** (N = 1247)	**Noncarriers** (N = 440)	**Heterozygotes** (N = 804)	**Homozygotes** (N = 263)
ARIA-E n (%)	379 (25.1)	266 (21.3)	73 (16.6)	192 (23.9)	113 (43.0)
Mild	123 (8.1)	89 (7.1)	26 (5.9)	62 (7.7)	34 (12.9)
Moderate	227 (15.0)	157 (12.6)	44 (10.0)	113 (14.1)	70 (26.6)
Severe	29 (1.9)	20 (1.6)	3 (0.7)	17 (2.1)	9 (3.4)
Symptomatic, n (%)	91 (6.0)	68 (5.5)	20 (4.5)	48 (6.0)	23 (8.7)
Mild	21 (1.4)	18 (1.4)	6 (1.4)	12 (1.5)	3 (1.1)
Moderate	51 (3.4)	38 (3.0)	12 (2.7)	26 (3.2)	13 (4.9)
Severe	19 (1.3)	12 (1.0)	2 (0.5)	10 (1.2)	7 (2.7)
ARIA-H n(%)	577 (38.2)	425 (34.1)	108 (24.5)	316 (39.3)	152 (57.8)
Mild	288 (19.1)	239 (19.2)	71 (16.1)	167 (20.8)	49 (18.6)
Moderate	101 (6.7)	70 (5.6)	14 (3.2)	56 (7.0)	31 (11.8)
Severe	188 (12.5)	116 (9.3)	23 (5.2)	93 (11.6)	72 (27.4)

Abbreviations: AACI = I5T-MC-AACI; ARIA = amyloid-related imaging abnormality; ARIA-E = ARIA- oedema/effusions; ARIA-H = ARIA-haemorrhage/haemosiderin deposition; LTE = long term extension; ICH = intracerebral haemorrhage; MRI = magnetic resonance imaging; N = number of participants; n = number of subjects with at least 1 AE; PC = placebo controlled.

ARIA-E in AACI-LTE (proposed indicated population)

Frequency

The incidence of ARIA-E in donanemab-treated participants was higher in the overall population (25.4%) than in the proposed indicated population (21.6%).

Radiographic Severity

As observed in the PC period, most (~92%) of ARIA-E observed were mild to moderate in severity. 1.6% had severe ARIA-E.

Symptomatic ARIA-E

Similar to the PC period,

- 71 (5.7%) donanemab-treated participants had symptomatic ARIA-E
- 198 (15.9%) donanemab-treated participants had asymptomatic ARIA-E.

The frequency of symptomatic ARIA-E was higher in carriers versus noncarriers.

Serious ARIA-E including deaths

Similar to the PC period, serious ARIA-E was reported in 16 (1.3%) of donanemab-treated patients. The frequency of serious ARIA-E was higher in donanemab-treated APOE ε4 carriers vs. noncarriers.

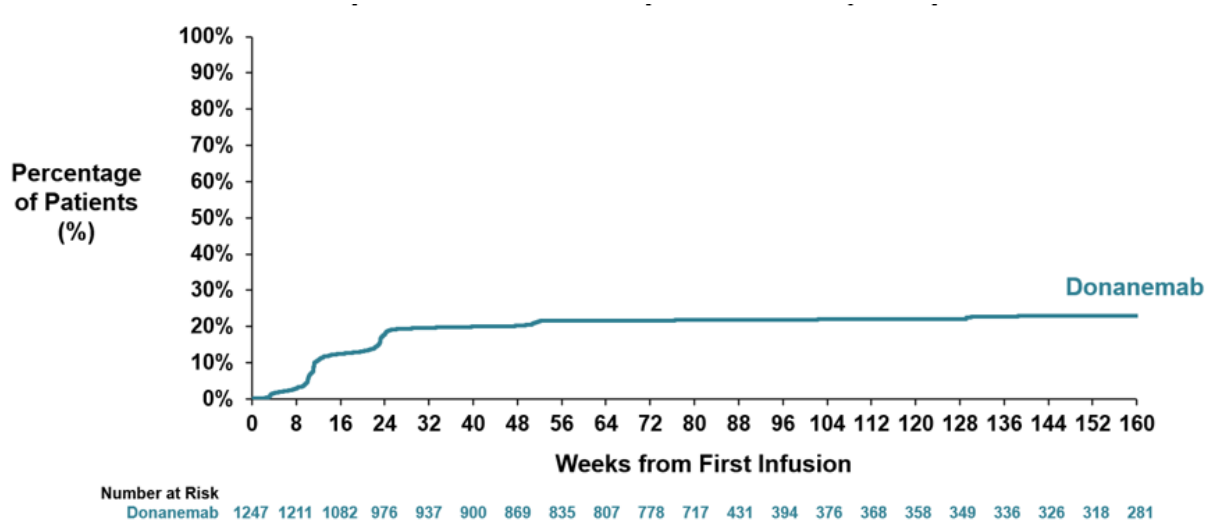
One participant with ARIA-E had a **fatal outcome due to ARIA-E**.

- A 70-to-80-year-old (APOE ε4 heterozygote) with hypertension, hyperlipidaemia, coronary artery disease, myocardial infarction, and prolactin-producing pituitary tumour, prostate cancer, and with ASS and donepezil as concomitant medications started on placebo. Screening MRI showed one microhaemorrhage. From Day 96 to Day 512, MRI remained unchanged. On Day 567, the patient started donanemab in the AACI-LTE. On Day 594 and Day 631, the patient's MRI scan remained unchanged. Last dose (24th dose; 5th infusion of donanemab in the AACI-LTE) was on Day 671. On Day 694, 23 days after the second dose of 1400 mg donanemab, the patient was hospitalised with difficulty in walking, heightened confusion, severe headache, nausea, dizziness, unstable gait, and visual impairment. Symptomatic ARIA-E was reported. On Day 696, the MRI showed a moderate T2 hyperintense lesion in the right occipital lobe with vasogenic oedema and mild mass effect. On Day 699, IV methylprednisolone (1000 mg/day) treatment was initiated for 5 days. On Day 704, methylprednisolone treatment was transitioned to prednisone. On Day 716, the patient's condition progressively worsened. MRI (Day 723) showed a decreased abnormal T2/FLAIR signal in the right occipital lobe with a resolution of surrounding mass effect and sulcal effacement. The patient was discharged to a nursing home facility and died on Day 730 due to ARIA-E.

Onset and Resolution of ARIA-E

Most ARIA-E events in donanemab-treated participants were first observed within 24 weeks of treatment initiation (Figure 26 below). No significant difference in time to onset of ARIA-E by genotype was observed.

Figure 26. Kaplan-Meier curve for time to first ARIA-E for population of heterozygotes and noncarriers based on safety MRI or TEAE cluster (AACI-PC +LTE period)



Recurrence of ARIA-E

The majority of participants with ARIA-E experienced a single episode and ~ 23% of donanemab-treated participants experienced more than one episode during the AACI-study.

ARIA-H in AACI-LTE (proposed indicated population)

Frequency

The incidence of ARIA-H (including isolated ARIA-H and concurrent AIRA-E/H) in donanemab-treated participants was higher in the overall population (38.3%) than the proposed indicated population (34.2%).

Radiographic Severity

As observed in the PC period, most (~73%) of ARIA-H observed were mild to moderate in severity. Of the participants receiving donanemab, 9.3% had severe ARIA-H.

Symptomatic ARIA-H

Similar to the PC period,

- 11 (0.9%) donanemab-treated participants had symptomatic ARIA-H
- 416 (33.4%) donanemab-treated participants had asymptomatic ARIA-H.

The frequency of symptomatic ARIA-H was higher in carriers versus noncarriers.

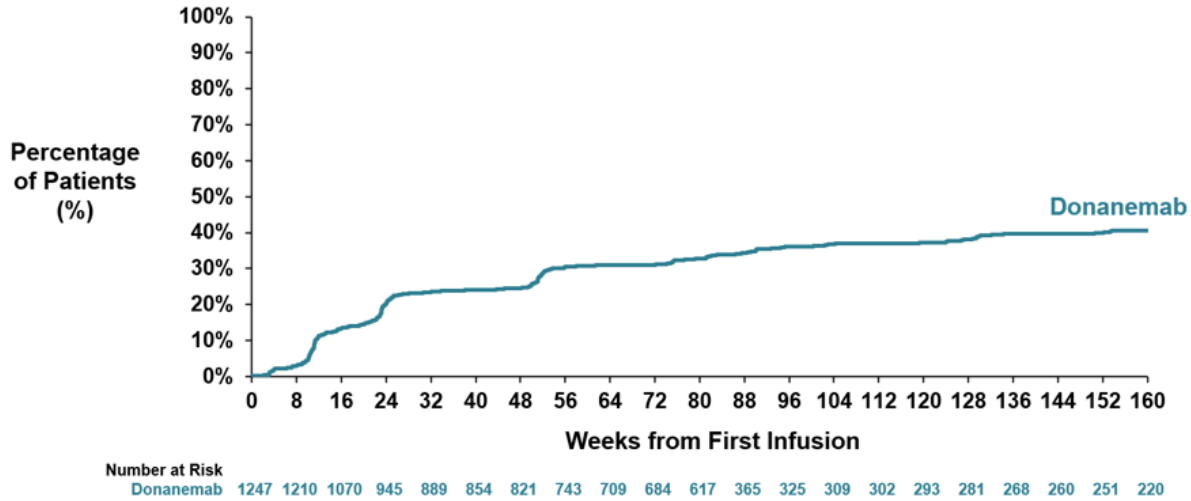
Serious ARIA-H including deaths

Serious ARIA-H was reported in 2 (0.2%) donanemab treated participants. The frequency of serious ARIA-H was higher in donanemab-treated APOE ε4 homozygotes, followed by noncarriers.

Onset of ARIA-H

Most ARIA-H events in donanemab-treated participants were first observed within 24 weeks of initiation of treatment (Figure 30). No significant difference in time to onset of ARIA-H by genotype was observed.

Figure 27. Kaplan-Meier curves for time to first ARIA-H for the proposed population of heterozygotes and noncarriers based on safety MRI or TEAE cluster (AACI-PC+ LTE period)



Abbreviations: AACI = I5T-MC-AACI; ARIA-H = amyloid-related imaging abnormality–haemorrhage or haemosiderin; LTE = long term extension; MRI = magnetic resonance imaging; PC = placebo controlled; TEAE = treatment emergent adverse event.

Recurrence of ARIA-H

The majority of participants with ARIA-H experienced a single episode and 38.4% of donanemab-treated participants experienced more than one episode of ARIA-H during the LTE period.

Intracerebral Haemorrhage > 1cm in AACI-LTE (proposed indicated population)

Frequency

Similar to the PC period, a total of 7 (0.6%) donanemab-treated participants reported macrohaemorrhage events.

Serious ICH > 1cm including deaths

2 serious cases of ICH >1 cm were reported that included one death in a participant treated with a thrombolytic medication:

A 70-80-year-old (APOE ε4 heterozygote) with no relevant medical history, randomly assigned to receive placebo in the AACI-PC on Day 1. On Day 503, the participant received the last dose of placebo and was enrolled to the AACI-LTE on Day 566 and started to receive donanemab. The last dose (24th dose) of the study drug in the study prior to SAE was on Day 693. On Day 702, the participant reported headache and was noted to have severe slurred speech. The participant was hospitalised with a diagnosis of acute ischaemic stroke. Result of the initial CT scan of the brain was negative, and a tele-neurology consultation recommended tissue plasminogen activator treatment. The participant received Tenecteplase and experienced altered mental status within an hour. Repeat CT scan showed multiple haemorrhages in bilateral hemispheres. The participant had no risk factors for ischaemic stroke; risk factors for ICH included recent elevated glucose level with no history of diabetes. After haemorrhage was detected, the participant received multiple coagulation factors and fibrinogen in an attempt to reverse the tenecteplase. On Day 706, the participant was removed from ventilatory support and died 3 hours later. Cause of death was reported as bilateral intraparenchymal haemorrhage and acute hypoxic respiratory failure. The presenting cerebrovascular accident was not rated as related to the study drug but the resulting haemorrhages from tenecteplase (reported as

tissue plasminogen activator) could have been made worse by CAA and amyloid removed by blinded study drug.

Long-Term Safety In Participants Treated Beyond 18 Months

In response to the EMA (D180 LoQ#27), the applicant provided a safety analysis in participants from study AACI-PC/LTE with more than 18 months of donanemab treatment with the data cut off 30 August 2024 (overall population). Overall, the safety profile of donanemab in participants with more than 18 months donanemab exposure is consistent with that observed in the placebo-controlled period, with reduced incidence rates of ARIA and IRR as expected.

Safety findings for participants with > 18 months of donanemab treatment in Study AACI-LTE were compared to those treated with donanemab for up to 18 months in AACI-PC.

A total of 172 participants continued to be treated with donanemab in Study AACI-LTE beyond the 18 months of the placebo-controlled period. The median number of infusions for participants continuing into the LTE period was 28.5 compared with 18 for those exposed to donanemab only in the PC period. 28 participants received 38 infusions or more.

Overall, two deaths were reported in the donanemab-treated participants that continued the treatment in the LTE period beyond 18 months. Both deaths were not ARIA- or ICH - related (passenger in a car accident and general health deterioration).

ARIA

Table 56 below provides a summary of frequency of ARIA events observed in the Study AACI-LTE compared with corresponding frequencies for events in Study AACI-PC.

Table 56. Summary of ARIA and intracerebral haemorrhage-related events study I5T-MC-AACI (PC + LTE); data cutoff = 30 August 2024

	AACI-PC (up to 18 months)		**AACI-PC and LTE (up to and beyond 18 Months)[a]**
	Placebo (N = 874) PYO = 1238.9 n (%) [OAIR]	**Donanemab (N = 853) PYO = 1176.5 n (%) [OAIR]**	**Donanemab (N = 172) (PYO =1238.9) n (%) [OAIR]**
ARIA Total events[b]	130 (14.9) [11.5]	315 (36.9) [36.2]	91 (52.9) [28.6]
ARIA-E[b]	18 (2.1) [1.5]	205 (24.0) [21.4]	45 (26.2) [11.2]
SAE	0 (0.0) [0.0]	13 (1.5) [1.1]	1 (0.6) [0.2]
Symptomatic[b,c]	1 (0.1) [0.1]	52 (6.1) [4.6]	9 (5.2) [1.8]
ARIA-H[b]	119 (13.6) [10.4]	269 (31.5) [29.1]	87 (50.6) [26.6]
SAE	0 (0.0) [0.0]	4 (0.5) [0.3]	0 (0.0) [0.0]
Symptomatic[c]	3 (0.3) [0.2]	10 (1.2) [0.9]	1 (0.6) [0.2]
Intracerebral haemorrhage greater than 1cm[d]	2 (0.2) [0.2]	3 (0.4) [0.3]	0 (0.0) [0.0]

Abbreviations: AE = adverse event; ARIA-E = amyloid-related imaging abnormalities-oedema; ARIA-H = amyloid related imaging abnormalities-haemorrhagic; CRF = case report form; LTE = long-term extension; MRI = magnetic resonance imaging; n = number of participants with at least 1 AE; N = number of participants; OAIR = incidence rates adjusted for observation time; PC = placebo controlled; PYO = patient-years of observation time; SAE = serious adverse event; TEAE = treatment-emergent adverse event.

a Includes events reported for donanemab-treated participants in both AACI-PC and AACI-LTE periods of Study AACI.

b Based on MRI or TEAE cluster output.

c Based on ARIA CRF for ARIA-E or AE reporting for ARIA-H.

d Based on TEAE cluster including cerebral haemorrhage and haemorrhagic stroke.

Safety from Study AACG: Supporting Data from Phase 2

Study AACG was a randomised Phase 2 study assessing safety, tolerability, and efficacy of donanemab in participants with early symptomatic AD, and intermediate brain tau load. A total of 272 participants were enrolled using eligibility criteria that incorporated flortaucipir and florbetapir PET scan imaging eligibility criteria. A total of 131 participants were randomised to donanemab and 126 were randomised to placebo. Safety data from this study was integrated with that from study AACI and presented as the Dona-PC safety analyses set in the original SCS.

Key safety findings from this study included:

- The overall incidence of deaths (0.8% vs. 1.6%), or participants reporting at least 1 SAE (17.6% each) or TEAE (90.8% vs. 90.4%), were not significantly different in donanemab-treated participants compared with placebo-treated participants.
- There was an overall greater incidence of discontinuations from study treatment (29.8% vs. 7.2%), or from study (16% vs. 7.2%), due to AEs for donanemab versus placebo.
- The most frequent TEAEs in ≥2% of participants, occurring in a statistically significantly higher proportion of donanemab-treated participants compared with placebo-treated participants, included ARIA-E (26.7% vs. 0.8%), superficial siderosis of CNS, nausea, and IRRs (6.9% vs.

0%). Most TEAEs were of mild to moderate severity. ARIA-H was reported for 30.5% and 7.2% of patients treated with donanemab versus placebo.

- The incidence of ARIA-H and/or ARIA-E based on MRI was higher in the donanemab group compared with placebo during the double-blind period. Most AEs of ARIA-E were asymptomatic. SAE of ARIA-E occurred in 1.5% of donanemab treated participants. The median time to resolution for ARIA-E in the donanemab group was 9.6 weeks. Both ARIA-E and ARIA-H occurred at a higher frequency in APOE ε4 carriers compared with noncarriers.

Infusion-related reactions were significantly more frequent in the donanemab group compared with the placebo group, and most events were fully resolved on the same day as onset. SAE of IRR occurred in 1.5% of donanemab-treated participants.

Post-marketing data consistent with donanemab safety profile

The applicant provided 9 months of post marketing data (02 July 2024 to 02 April 2025), mainly from US and Japan spontaneous reporting, which show consistency with the safety profile of donanemab in the clinical programme. Of note, donanemab was approved in both the US and Japan for the treatment of patients with mild cognitive impairment or mild dementia stage of disease regardless of APOE ε4 genotype.

The LSS is the global database used within the Global Patient Safety department for the collection, storage, and reporting of AEs to regulatory authorities, investigators, and internal departments. The LSS global database contains serious and nonserious AEs reported from the post-marketing experience, including spontaneous reports, literature reports, regulatory authority reports, and reports from noninterventional studies.

The safety data from post-marketing experience for donanemab is proactively reviewed twice a month by a cross-functional development safety team including safety physicians, clinical safety scientists, Global Patient Safety Medical reviewers, and pharmacoepidemiologists.

There were no new signals or risks identified or evaluated for donanemab since the International Birth Date on 02 July 2024.

Postmarketing information focusing on reported events of ARIA (including ARIA-E and ARIA-H) and ICH >1 cm is based on a search of the LSS for serious and nonserious events that were received from IBD (02 July 2024) through 02 April 2025. The search was performed using MedDRA preferred terms outlined in Table 57 below.

Table 57. Search strategies used to collect post-marketing data

Adverse Event	Search Strategy
ARIA-E (cerebral oedema/effusion)	Preferred terms: Amyloid related imaging abnormalities, Amyloid related imaging abnormality-oedema/effusion, Brain oedema, Vasogenic cerebral oedema.
ARIA-H	Preferred terms: Amyloid related imaging abnormality-microhaemorrhages and haemosiderin deposits, Brain stem microhaemorrhage, Cerebellar microhaemorrhage, Cerebral haemosiderin deposition, Cerebral microhaemorrhage, Superficial siderosis of central nervous system, Thalamic microhaemorrhage.
ARIA unspecified as either -E or -H	Preferred term: Amyloid related imaging abnormalities
Intracerebral haemorrhage greater than 1cm	Preferred terms: Cerebral haemorrhage, Haemorrhagic stroke.

Abbreviations: ARIA = amyloid-related imaging abnormality; ARIA-E = ARIA- oedema/effusions; ARIA-H = ARIA-haemorrhage/haemosiderin deposition

It is also important to note that as ARIA (including ARIA-E, brain oedema, ARIA-H, cerebral microhaemorrhage, superficial siderosis) and ICH are important medical events, and as post-marketing cases often contain limited information, these events may conservatively be considered as serious by the company. Consequently, this is reflected in the number of serious ARIA and ICH events presented from the post-marketing experience.

Postmarketing exposure
Worldwide sales of donanemab have been collected for the cumulative period ending 31 March 2025, since the sales data are only available in complete months (Table 65 below).

As of 31 March 2025, a total of 52,224 vials (18,278 g) of donanemab had been sold worldwide.

The number of participants cannot be adequately estimated at this time due to small-volume sales and limited period of market availability. It should also be noted that early sales of a newly marketed product may often reflect stocking by wholesalers as opposed to actual patient exposure. Trending sales data across several periodic report periods will give an indication of the level of use of the product in the patient population.

Post-marketing ARIA

Overall, 202 events of ARIA (in 168 reports) have been reported in the LSS, including 87 events of ARIA-E (including brain oedema), 84 events of ARIA-H (including cerebral microhaemorrhage and superficial siderosis) and 31 events of ARIA unspecified as either -E or -H.

Post-marketing ARIA-E (cerebral oedema/effusion)

87 events of ARIA-E (including brain oedema) have been reported in the LSS.

When time-to-onset was available, ARIA-E events occurred early in treatment (within 2 months). Radiographic severity was available for 38% of the reports (33 events) with the majority being mild or moderate (26/33 [79%]). In the majority of events with known action, donanemab was either interrupted or withdrawn (51/61 [84%]) which is aligned with the instructions provided in labelling. Of the ARIA-E events with known outcome, 57% (21/37) recovered or were recovering, and 43% (16/37) had not yet recovered. When APOE ε4 genotype was known, 24% (4/17) of ARIA-E occurred in noncarriers, 47% (8/17) in heterozygotes, and 29% (5/17) in homozygotes.

Of the 87 ARIA-E events, 31% (27 events) were symptomatic with the most reported symptoms being headache and confusion. Additional symptoms associated with ARIA-E included cognitive disorder, dizziness/balance issues, vision changes and gait disturbances. When APOE ε4 status was reported, the majority of the symptomatic ARIA-E events related to APOE ε4 carriers (8/9 [89%]), of whom 5 were heterozygotes and 3 were homozygotes.

Of the 87 ARIA-E events, 13% (11 events) were received as serious reports (all serious due to hospitalisation and one also reported as life-threatening). The APOE ε4 genotype was known in 4 of the 11 reported serious ARIA-E events with 1 patient being noncarrier, 1 heterozygote and 2 homozygotes. These 11 reported SAEs were mostly symptomatic (mostly headache and confusion; also, aphasia/dysphasia, and seizure in 1 case). Additionally, 64% (56 events) were classified as serious by the company as ARIA is considered an important medical event and may conservatively be classified as medically important by the company when limited information is available.

There has been one death with unknown cause in a patient (APOE ε4 status unknown) who had a serious event of brain oedema concurrent with cerebral haemorrhage (reported as small brain bleed).

Post-marketing ARIA-H (cerebral microhaemorrhage and superficial siderosis)

84 events of ARIA-H (including cerebral microhaemorrhage and superficial siderosis) have been reported in the LSS and 39% (33 events) occurred concurrently with ARIA-E.

When time-to-onset was available, ARIA-H events occurred early in treatment (within 3 months). Radiographic severity was available for 36% of the reports (30 events) with ARIA-H being mostly mild or moderate (25/30 [83%]). In the majority of events with known action, donanemab was either interrupted or withdrawn (52/59 [88%]) which is aligned with the instructions provided in labelling. Among the reports with known outcome, 49% (17/35) were recovered, recovering or stabilised and 51% (18/35) were reported as not recovered. When APOE ε4 genotype was known, 21% (3/14) of ARIA-H occurred in noncarriers, 50% (7/14) in heterozygotes, and 29% (4/14) in homozygotes.

In 6% of the reports (5 events) patients were receiving a concomitant antiplatelet agent (all aspirin), and in 2% of the reports (2 events) patients were receiving concomitant anticoagulants (apixaban and warfarin). There were no reports of ARIA-H in which the patient had received a thrombolytic.

Of the 84 ARIA-H events, 26% (22 events) were symptomatic with the most reported symptom being headache followed by gait disturbance/inability to ambulate. A majority of the 22 reported symptomatic ARIA-H events were concurrent with ARIA-E (15/22 [68%]). When APOE ε4 status was reported, the majority of the symptomatic ARIA-H events related to APOE ε4 carriers (6/7 [86%]), of whom 2 were heterozygote and 4 were homozygote.

Of the 84 ARIA-H events, 7% (6 events) were received as serious reports (all serious due to hospitalisation). The APOE ε4 genotype was known in 2 of the 6 reported serious ARIA-H events with 1 patient being noncarrier and 1 homozygote. These 6 reported serious events were all symptomatic (mostly headache; also, aphasia/dysphasia and seizure in 1 case) and all concurrent with ARIA-E. Additionally, 69% (58 events) were classified as serious by the company as ARIA is considered an important medical event and may be conservatively classified as medically important by the company when limited information is available.

There has been one death due to unknown cause following a fall and head injury, which occurred in a patient (APOE ε4 noncarrier) who had a preceding event of non-serious, mild, asymptomatic ARIA-H.

Post-marketing ARIA unspecified type

31 events of ARIA unspecified as either -E or -H have been reported in the LSS.

When time-to-onset was available, ARIA events occurred early in treatment (within 3 months). Radiographic severity was known only for 13% of the reports (4 events) with all of them being mild. In a majority of events with known action, donanemab was either interrupted or withdrawn (10/13 [77%]), which is aligned with the instructions provided in labelling. Information on the event outcome was generally lacking and APOE ε4 status was available only for one patient who was homozygote.

Of the 31 ARIA events, 23% (7 events) were symptomatic with the most reported symptoms being headache and brain fog; unspecified stroke-like symptoms were also reported in one case.

None of the 31 ARIA events were received as serious reports; and 74% (23 events) were classified as serious by the company as ARIA is considered an important medical event and may be conservatively classified as medically important by the company when limited information is available.

There have been no fatalities in patients who had ARIA events of unspecified type.

Post-marketing ICH > 1 cm

24 events of ICH have been reported in the LSS. These were all reports of cerebral haemorrhage.

Of the 24 events, 25% (6 events) were received as serious reports (all serious due to hospitalisation; one also reported as life-threatening, and another also serious for death). Additionally, 71% (17 events) were classified as serious by the company as cerebral haemorrhage is considered an important medical event.

Time-to-onset was available only in 13% of the reports (3 events), and these cerebral haemorrhage events occurred early in treatment (within 3 months). In the majority of events with known action, donanemab was either interrupted or withdrawn (13/14 [93%]) which is aligned with the instructions provided in labelling. APOE ε4 status was provided in 13% of the reports (3 patients) with 2 patients being heterozygotes and 1 homozygote. While information on event outcome was generally lacking, one event of cerebral haemorrhage reported a fatal outcome in a patient APOE ε4 heterozygote.

There were no reports of cerebral haemorrhage in which the patient was receiving a concomitant antiplatelet, anticoagulant or had received a thrombolytic.

The size of the cerebral haemorrhage was confirmed to be > 1 cm for one of the 24 events of cerebral haemorrhage, while the majority (88%) were received with a verbatim term of brain bleed and no details about the size of the brain bleed. Among the 24 events of cerebral haemorrhage:

- The event with confirmed size was reported as a 1.3-centimeter-wide brain bleed. This consumer report concerned a 70-to-80-year-old patient (APOE ε4 status unknown) who underwent MRI showing a 1.3-centimeter-wide brain bleed, after the 2nd infusion of donanemab and one month 25 days after starting therapy. Donanemab was interrupted, which is aligned with the instructions provided in labelling, and a follow-up MRI was planned. Past medical history, concomitant medications, information on corrective treatment and outcome of the event were unknown.
- One event was reported as "two macrohaemorrhages". This report received from a neurologist did not provide the size of the cerebral haemorrhage, however it reported that the patient was found to have developed two macrohaemorrhages. Further details, including patient's demographics, APOE ε4 status, medical history, concomitant medications and event outcome, are not available and the reporting neurologist declined to provide additional follow-up information.
- One event was reported as inoperable ICH; this is a fatal report of cerebral haemorrhage, which occurred in an 80-to-90-year-old patient APOE ε4 heterozygote (further discussed below).

  21 events were received with a verbatim term of brain bleed (8 events) or brain bleeding (4 events) or small/minor/mild brain bleed (6 events) or spots of bleeding (2 events) or leakage from blood vessel (1 event), and no details were provided about the size of the cerebral haemorrhage event.
- Of these, 8 were concurrent with ARIA events (ARIA-E, brain oedema or ARIA unspecified), and included one report of small brain bleed concurrent with brain oedema and subsequent death due to unknown cause (further discussed below)
    - Four of the 21 events reported symptoms including confusion (in 1 report), unsteady balance (in 1 report), headache and flu-like symptoms (in 1 report) and migraine, nausea, vertigo, visual impairment (in 1 report).
    - An additional event of brain bleed was concurrent with a small stroke. No further details are available currently and attempts to obtain additional follow-up information are being made.

Post-marketing Fatalities Reported in Patients with ARIA-E, ARIA-H, or ICH

There have been 3 reports of deaths in patients who experienced ARIA-E, ARIA-H or ICH. In these 3 reports, one patient was APOE ε4 heterozygote, one was APOE ε4 noncarrier, and one was of unknown APOE ε4 status. For 2 of these fatalities, the cause of death was unknown (Table 58).

Table 58. Fatalities reported during the post-marketing period

Patient age/Sex/APOE carrier status/ Reporter	**Patient's relevant medical history**	**Time to onset**	**Case Details**
70-80 years/ / APOE ε4 noncarrier/ physician	Unknown	Unknown (after 1st infusion)	This spontaneous report concerns a 70-80-year-old patient APOE ε4 noncarrier who experienced non-serious mild asymptomatic ARIA-H, after 1st donanemab infusion (unknown time-to-onset). Donanemab was held for more than 6 weeks, and a repeat magnetic resonance imaging (MRI) showed stable and unchanged mild ARIA-H. While donanemab was still interrupted, on an unknown date, this patient experienced a fall, a head injury (reported as "traumatic subdural"), and then died. The cause of death was unknown, and autopsy results were not provided. The reporting physician did not relate the events of death, fall and traumatic subdural with donanemab therapy. Past medical history and concomitant medications were unknown.
70-80 years/ / APOE ε4 status unknown/ physician (neurologist)	Unknown	Unknown (after 1st infusion)	This spontaneous report concerns a 70-80-year-old patient with APOE ε4 status unknown, who developed unsteady balance after 1st infusion of donanemab (unknown time-to-onset). A follow-up MRI revealed brain oedema (reported as "extensive brain swelling") and cerebral haemorrhage (reported as "small brain bleed"), and the patient was hospitalised (both events were also serious as life-threatening). The brain swelling had initially worsened requiring the patient to be admitted in intensive care unit (ICU) and placed on ventilator. The patient's condition had later improved, and the patient was out of ICU and taken off ventilator. On an unknown date while still hospitalised, the patient died. The cause of death was unknown, and autopsy results were not provided. The events of small bleed in brain, extensive swelling in brain and unsteady balance were recovering at the time of death. The neurologist related this patient's fatality to donanemab infusion. Past medical history and concomitant medications were unknown.

80-90 years/ / APOE ε4 carrier heterozygote/ physician	Mild cognitive impairment	Unknown (2 weeks after 3rd infusion)	This spontaneous report concerns an 80-90-year-old APOE ε4 carrier heterozygote, who was found unconscious and taken to hospital due to inoperable intracerebral haemorrhage, approximately 2 weeks after the 3rd infusion of donanemab (unknown time-to-onset from 1st infusion). Two previous MRIs (reported as "initial" and "subsequent") performed prior to the hospitalisation were both negative. There are no further details about the hospital course and 5 days after admission the patient passed away due to intracerebral haemorrhage. It was unknown if an autopsy was performed. The reporting physician related the intracerebral haemorrhage to donanemab therapy. Reportedly, the patient was not on any type of blood thinners or acetylsalicylic acid.

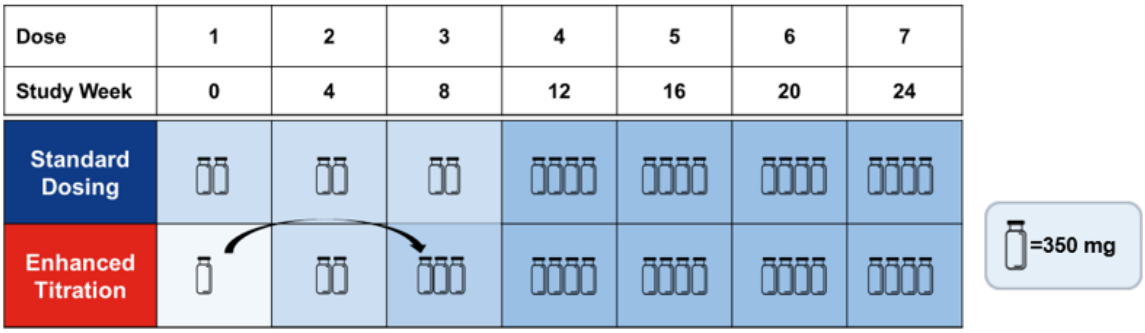
In conclusion, with regards to the risk of ARIA, the safety profile of donanemab in the post-marketing setting is consistent with that observed during clinical trials.

Safety in Study AACQ (TRAILBLAZER-ALZ6) and Donanemab-Modified Titration Regimen

The applicant conducted Study AACQ (TRAILBLAZER-ALZ6) as part of continued efforts to reduce the risk of ARIA. During the original procedure, the applicant provided a summary of the 24-week primary outcome data and 52-week data (Wang et al., 2025). This study, recently completed with 76-week data, investigated the effect of different donanemab dosing regimens on ARIA-E and amyloid lowering in adults with early symptomatic AD.

The modified titration arm dosing differed from the standard titration arm simply by the timing of a single vial (350 mg), which was removed from the first infusion and added to the third infusion (Figure 28). Total donanemab exposure in the first 3 months remained identical. The dosing level and frequency were exactly the same at and after Week 12.

Figure 28. Same total amount of drug is delivered in the modified titration over the first 3 visits, with identical dosing thereafter



The modified titration arm met the 24-week primary outcome with 94% probability of achieving ≥20% RRR versus the standard arm (Wang et al., 2025). ARIA-E frequencies for standard and modified titration arms were 23.7% and 13.7%, respectively in the overall population and 19.9% and 13.1% in the proposed indicated population. Furthermore, the modified titration arm showed a significantly lower severity of ARIA-E and risk of cortical superficial siderosis compared to the standard arm. Importantly, the standard and modified titration arms had a similar amyloid reduction from baseline as assessed by PET scans (adjusted mean change at 24 weeks: 58.8 CL versus 56.3 CL, respectively).

The 52-week results (presented below) were consistent with the 24-week results suggesting that ARIA-E was reduced rather than delayed in the modified titration arm (Wang et al. 2025).

At 76 weeks (manuscript in preparation), in the overall population, ARIA-E frequencies were 24.2% (standard) and 15.6% (modified titration), with the modified titration arm showing 35% relative risk reduction of ARIA-E versus the standard arm. There were no scheduled MRIs at 76 weeks. No additional ARIA-E events occurred between 52 and 76 weeks in the modified titration arm. There was one new participant with ARIA-H (a non-serious event)in the modified titration arm between 52 and 76 weeks.

Overview of ARIA-E, ARIA-H, and ICH > 1cm at 52 Weeks in Study AACQ

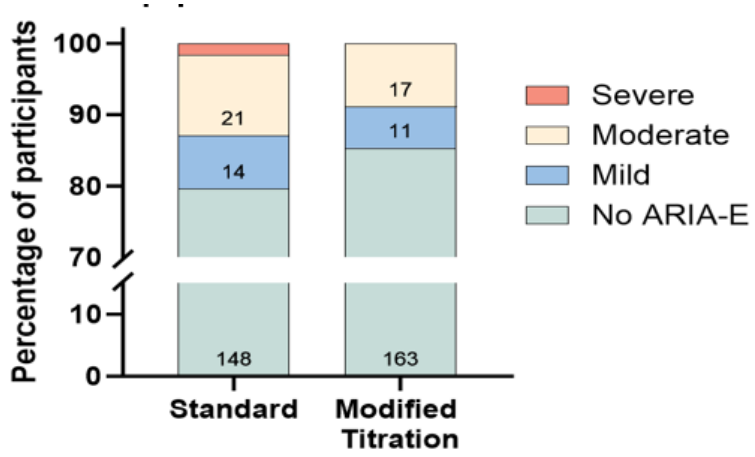
ARIA-E in Study AACQ

In the overall population, the modified titration group at Week 52 showed a 35% relative risk reduction of ARIA-E compared with the standard dosing group, with an 87% probability that the relative risk reduction was at least 20%.

In the proposed indicated population, in the modified titration arm (as shown in Table 59)

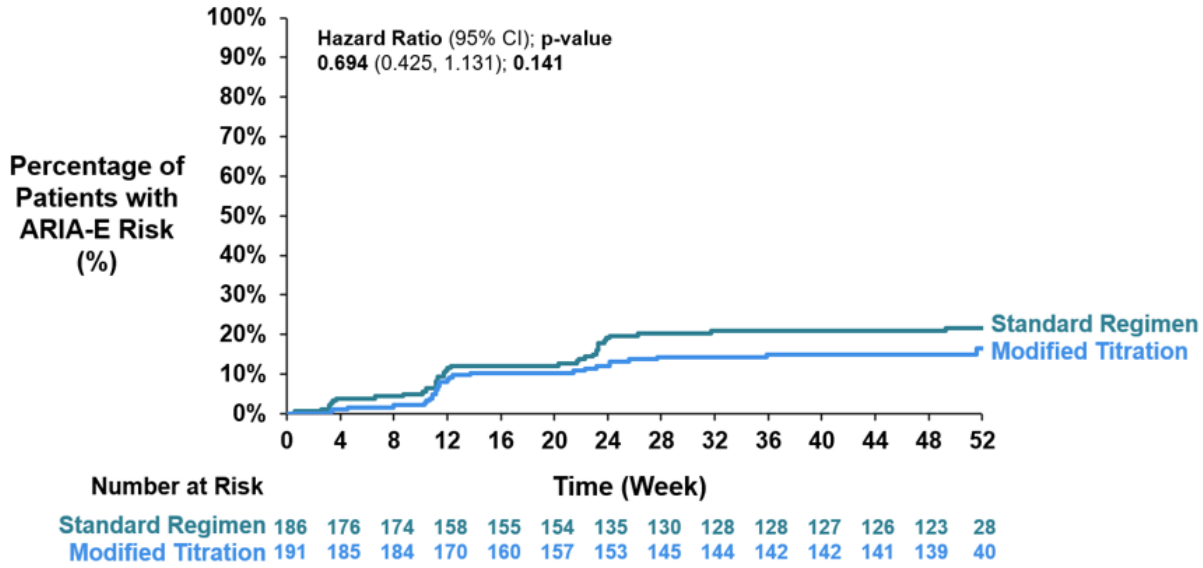
- The incidence of ARIA-E was 14.7%
- All cases of ARIA-E were mild to moderate in radiographic severity (Figure 29)
- 6 (3.1%) participants had symptomatic ARIA-E
- Serious ARIA-E was reported in 1 (0.5%) participant
- There were no ARIA-E related deaths
- Most ARIA-E events were first observed within 24 weeks (Figure 30).

Figure 29. ARIA-E radiographic severity in the modified titration arm vs standard arm, indicated population



Abbreviations: ARIA-E = amyloid-related imaging abnormality–oedema/effusion

Figure 30. Kaplan-Meier curves for time to first ARIA-E for the proposed indicated population (52-week)



Abbreviations: ARIA-E = amyloid related imaging abnormalities- oedema/effusion; CI = confidence interval.

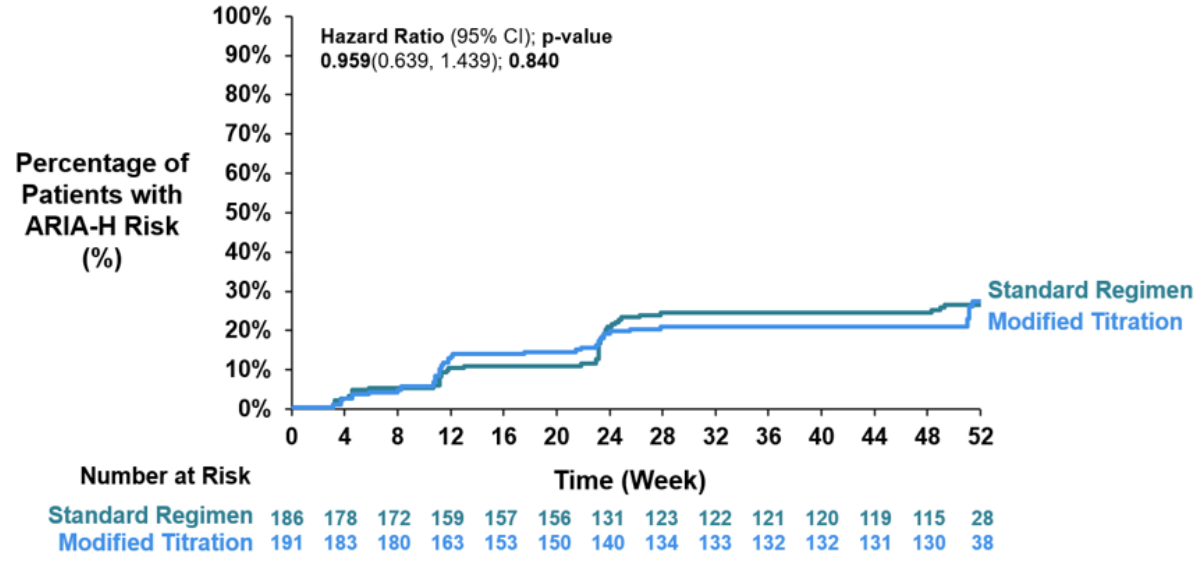
ARIA-H in Study AACQ (in the proposed indicated population)

In the modified titration arm (as shown in Table 23):

- The incidence of ARIA-H was 24.6%
- Approximately 87% of ARIA-H cases were mild to moderate in severity, 3.1% had severe ARIA-H (Table 24).
- There were no participants with SAEs of ARIA-H, or deaths due to ARIA-H

Most ARIA-H events in the modified titration group were first observed within 24 weeks of initiation of treatment (Figure 31).

Figure 31. Kaplan-Meier curves for time to first ARIA-H for the proposed indicated population



Abbreviations: ARIA-H= amyloid related imaging abnormalities-haemorrhage or haemosiderin; CI = confidence interval.

ICH > 1 cm in Study AACQ (proposed indicated population)

Two participants in the modified titration arm had ICH > 1cm:
- For one participant (noncarrier of APOE4): ICH event was asymptomatic and identified after six infusions (6 total; 3 donanemab and 3 placebo) were received by the participant, donanemab was withdrawn, and participant completed the study.

- For the other participant (APOE4 heterozygote): 70-80-year-old , received 9 infusions, 6 were donanemab, and the last dose was 1400 mg donanemab (Day 141). MRI at Day 150 showed mild ARIA-E and 6 new microhaemorrhages in the right parietal region. On Day 157, the participant presented with left hemiparesis, seizure-like activity, and was diagnosed with severe acute right middle cerebral artery stroke and was admitted to the hospital. As a treatment for acute right middle cerebral artery stroke, the participant received i.v. tenecteplase. On Day 158, head CT showed large right cerebral hemispheric intraparenchymal haemorrhage with mass effect. On Day 159, the participant died due to intraparenchymal haemorrhage. The SAE of "large right cerebral intraparenchymal haemorrhage" was not rated as related to study treatment. The SAE of "middle cerebral artery stroke" was rated as related to the study treatment.

Table 59. Overview of ARIA and ICH>1cm in overall population, all APOE ε4 genotypes, and proposed indicated population in study AACQ at 52 weeks based on MRI and TEAE cluster

	Overall		**Heterozygotes + Noncarriers**		**Noncarrier**		**Heterozygotes**		**Homozygotes**	
	Standard Dosing N = 207 n (%)	**Modified titration N = 212 n (%)**	**Standard Dosing N = 186 n (%)**	**Modified titration N= 191 n (%)**	**Standard Dosing N = 72 n (%)**	**Modified titration N = 75 n (%)**	**Standard Dosing N = 112 n (%)**	**Modified titration N = 115 n (%)**	**Standard Dosing N = 21 n (%)**	**Modified titration N = 21 n (%)**
Any ARIA (either E or H)	71 (34.3)	61 (28.8)	58 (31.2)	55 (28.8)	17 (23.6)	19 (25.3)	41 (36.6)	36 (31.3)	13 (61.9)	6 (28.6)
Any SAE of ARIA (either E or H)	0	1 (0.5)	0	1 (0.5)	0	1 (1.3)	0	0	0	0
Deaths associated with any ARIA/ICH >1cm	0	1 (0.5)	0	1 (0.5)	0	0	0	1 (0.9)	0	0
ARIA-E	50 (24.2)	33 (15.6)	38 (20.4)	28 (14.7)	11 (15.3)	10 (13.3)	27 (24.1)	18 (15.7)	12 (57.1)	5 (23.8)
Asymptomatic	40 (19.3)	27 (12.7)	29 (15.6)	22 (11.5)	11 (15.3)	8 (10.7)	18 (16.1)	14 (12.2)	11 (52.4)	5 (23.8)
Symptomatic	10 (4.8)	6 (2.8)	9 (4.8)	6 (3.1)	0	2 (2.7)	9 (8.0)	4 (3.5)	1 (4.8)	0
SAE of ARIA-E	0	1 (0.5)	0	1 (0.5)	0	1 (1.3)	0	0	0	0
Recurrent ARIA-E	13 (6.3)	4 (1.9)	9 (4.8)	4 (2.1)	2 (2.8)	3 (4.0)	7 (6.3)	1 (0.9)	4 (19.0)	0
ARIA-H	57 (27.5)	53 (25.0)	47 (25.3)	47 (24.6)	12 (16.7)	14 (18.7)	35 (31.3)	33 (28.7)	10 (47.6)	6 (28.6)
Asymptomatic	57 (27.5)	52 (24.5)	47 (25.3)	46 (24.1)	12 (16.7)	14 (18.7)	35 (31.3)	32 (27.8)	10 (47.6)	6 (28.6)
Symptomatic	0	1 (0.5)	0	1 (0.5)	0	0	0	1 (0.9)	0	0
Isolated ARIA-H[a]	19 (9.2)	28 (13.2)	18 (9.7)	27 (14.1)	4 (5.6)	9 (12.0)	14 (12.5)	18 (15.7)	1 (4.8)	1 (4.8)
Concurrent ARIA-H (with ARIA-E)[ab]	34 (16.4)	23 (10.8)	26 (14.0)	19 (9.9)	5 (6.9)	5 (6.7)	21 (18.8)	14 (12.2)	8 (38.1)	4 (19.0)
SAE of ARIA-H	0	0	0	0	0	0	0	0	0	0
Recurrent ARIA-H	22 (10.6)	15 (7.1)	16 (8.6)	12 (6.3)	4 (5.6)	5 (6.7)	12 (10.7)	7 (6.1)	6 (28.6)	3 (14.3)
ICH > 1cm	1 (0.5)	2 (0.9)	1 (0.5)	2 (1.0)	0	1 (1.3)	1 (0.9)	1 (0.9)	0	0
SAE of ICH > 1cm based on TEAE cluster	0	1 (0.5)	0 (0.0)	1 (0.5)	0	0	0	1 (0.9)	0	0

a Based on MRI only
b Concurrence is defined as ARIA-E and ARIA-H occurring on the same MRI.

Table 60. ARIA radiographic severity in overall population, all APOE ε4 genotypes, and proposed indicated population in study AACQ at 52 weeks

	Overall		**Heterozygotes + Noncarriers**		**Noncarriers**		**Heterozygotes**		**Homozygotes**	
Any ARIA Event by Week 52, n (%)	Standard Dosing N = 207	Modified titration N = 212	Standard Dosing N = 186	Modified titration N = 191	Standard Dosing N = 72	Modified titration N = 75	Standard Dosing N = 112	Modified titration N = 115	Standard Dosing N = 21	Modified titration N = 21
ARIA-E	50 (24.2)	33 (15.6)	38 (20.4)	28 (14.7)	11 (15.3)	10 (13.3)	27 (24.1)	18 (15.7)	12 (57.1)	5 (23.8)
Mild	17 (8.2)	13 (6.1)	14 (7.5)	11 (5.8)	6 (8.3)	4 (5.3)	8 (7.1)	7 (6.1)	3 (14.3)	2 (9.5)
Moderate	29 (14.0)	20 (9.4)	21 (11.3)	17 (8.9)	4 (5.6)	6 (8.0)	17 (15.2)	11 (9.6)	8 (38.1)	3 (14.3)
Severe	4 (1.9)	0	3 (1.6)	0	1 (1.4)	0	2 (1.8)	0	1 (4.8)	0
Symptomatic	10 (4.8)	6 (2.8)	9 (4.8)	6 (3.1)	0	2 (2.7)	9 (8.0)	4 (3.5)	1 (4.8)	0
Mild	2 (1.0)	1 (0.5)	2 (1.1)	1 (0.5)	0	0	2 (1.8)	1 (0.9)	0	0
Moderate	6 (2.9)	5 (2.4)	5 (2.7)	5 (2.6)	0	2 (2.7)	5 (4.5)	3 (2.6)	1 (4.8)	0
Severe	2 (1.0)	0	2 (1.1)	0	0	0	2 (1.8)	0	0	0
ARIA-H	55 (26.6)	53 (25.0)	45 (24.2)	47 (24.6)	10 (13.9)	14 (18.7)	35 (31.3)	33 (28.7)	10 (47.6)	6 (28.6)
Mild	30 (14.5)	35 (16.5)	27 (14.5)	34 (17.8)	9 (12.5)	10 (13.3)	18 (16.1)	24 (20.9)	3 (14.3)	1 (4.8)
Moderate	12 (5.8)	10 (4.7)	9 (4.8)	7 (3.7)	1 (1.4)	2 (2.7)	8 (7.1)	5 (4.3)	3 (14.3)	3 (14.3)
Severe	13 (6.3)	8 (3.8)	9 (4.8)	6 (3.1)	0	2 (2.7)	9 (8.0)	4 (3.5)	4 (19.0)	2 (9.5)

Abbreviations: ARIA = amyloid-related imaging abnormality; N = number of participants; n = number of subjects with at least 1 AE.

Modified Titration PK/PD Comparable to Standard Titration Regimen

As described in previous responses in the original procedure, the modified titration regimen achieved comparable PK/PD at 24 and 52 weeks as the standard dosing regimen in Study AACQ. Across APOE ε4 genotypes, exposure (PK) and amyloid plaque reduction did not differ. The PK/PD data from the modified titration regimen supports bridging between the standard dosing regimen and the modified titration:

The planned and observed cumulative doses (0 to 12 weeks), cumulative AUC (0-12 weeks), and average concentration at steady state (Cav,ss) for the standard dosing and enhanced titration regimens of Study AACQ were similar and overlapping. Exposure (Cav,ss) noninferiority, defined as the lower bound of 90% CI for the geometric mean ratio ≥0.8 for enhanced titration compared with standard titration, was demonstrated (Table 61).

Donanemab final population PK model with covariates of weight and antidrug antibody titre described the Week 52 AACQ data. Figure 32 depicts the overlapping distributions of cumulative AUC (0-12 weeks) from individual participants in Study AACQ standard regimen and modified titration dosing regimen. Even though there was intrinsic variability in the individual observed cumulative AUC (0-12 weeks), the distributions of standard and modified titration regimens largely overlap, and support bridging based on exposure of donanemab between the two dosing regimens in Study AACQ.

Similar conclusions are drawn comparing the observed cumulative AUC (0-12 weeks) from standard (N=206) and modified titration (N=212) dosing and those simulated from a larger sample size (N=10,000) using the final population PK model (Figure 33).

The correlation between lower amyloid levels and clinical efficacy provides increased confidence in applying the enhanced titration with PK comparability to a meaningful PD effect demonstrating equivalent amyloid lowering to the standard titration.

Table 61. Exposure metrics for standard dosing and enhanced titration dosing regimens

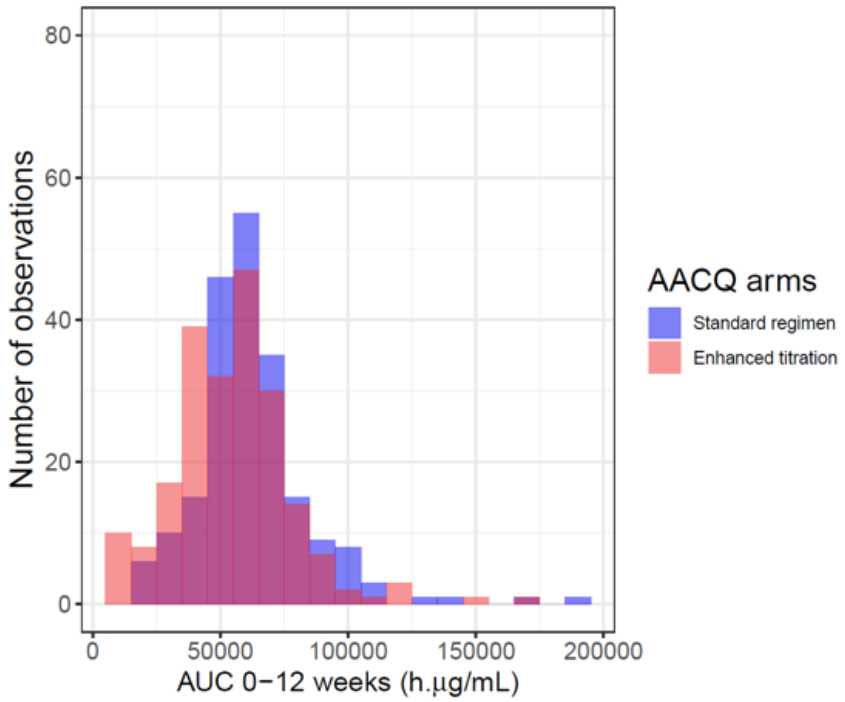
Outcome	Unit	Dosing Regimen	
		Standard Regimen	Enhanced Titration Regimen
Planned cumulative dose amount (0-12 weeks)	mg	3500	3500
Observed cumulative dose amount (0-12 weeks), N	mg	3123, 206	3015, 212
AUC(0-12 weeks)			
Geometric mean (95% CI)	µg*hr/mL (95% CI)	69,600 (64,800-73,050)	67,300 (62,000-70,250)
Test for noninferiority (95% CI)	GMR (95% CI)	–	0.967 (0.938-0.982)
Geometric mean (90% CI)	µg*hr/mL (90% CI)	69,600 (65,200-72,300)	67,300 (62,500-69,600)
Test for noninferiority (90% CI)	GMR (90% CI)	–	0.967 (0.942-0.979)
$C_{av,ss}$			
Geometric mean (95% CI)	µg/mL (95% CI)	63.1 (58.1-65.85)	63.0 (58.0-65.85)
Test for noninferiority (95% CI)	GMR (95% CI)	–	0.998 (0.973-1.029)
Geometric mean (90% CI)	µg/mL (90% CI)	63.1 (58.6-64.8)	63.0 (58.6-64.9)
Test for noninferiority (90% CI)	GMR (90% CI)	–	0.998 (0.979-1.026)

$C_{trough,ss}$			
Geometric mean (90% CI)	µg/mL (90% CI)	9.91 (9.44-10.8)	10.2 (9.55-10.8)
GMR (90% CI)[a]	GMR (90% CI)	–	1.029 (0.936-1.089)

Abbreviations: AUC(0-12 weeks) = area under the curve (0-12 weeks); $C_{av,ss}$ = average drug concentration at steady state, evaluated from Week 12 onward; CI= confidence interval; $C_{trough,ss}$ = minimum observed drug concentration during a dosing interval at steady state; GMR=geometric mean ratio; N = number of participants.

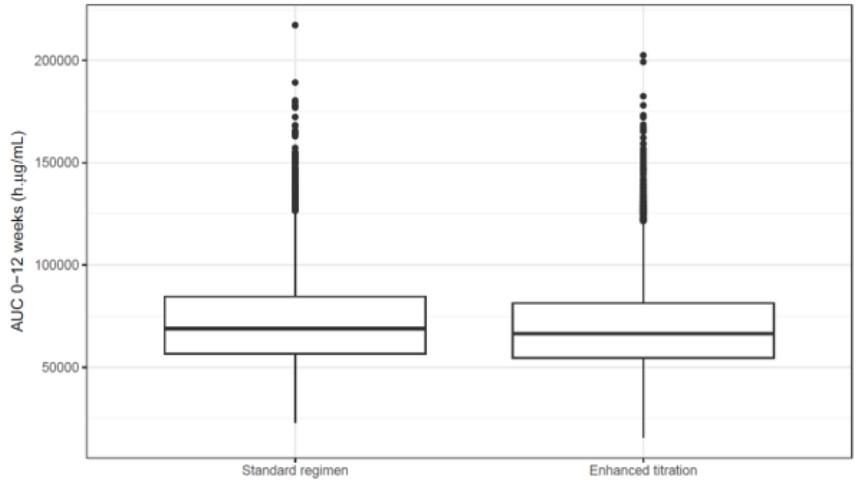
[a] The GMR (95% CI) and (90% CI) were generated using sampling from the bootstrapped CI of the post hoc population PK parameters, similarly to Wang et al. (2024).

Figure 32. Comparison of observed cumulative AUC (0-12 weeks) from standard dosing regimen and modified titration regimen



Abbreviations: AACQ = Study I5T MC-AACQ; AUC (0-12 weeks) = area under the curve (0 to 12 weeks)

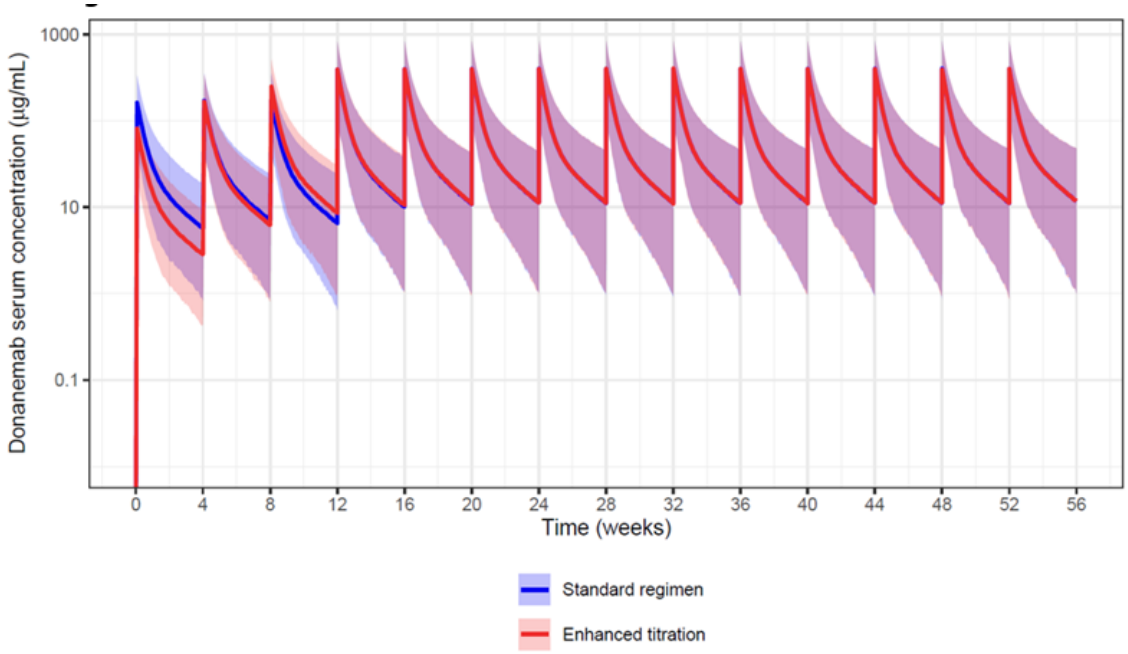
Figure 33. Comparing cumulative AUC (0-12 weeks) from standard and modified titration dosing simulated using the final population PK model



Abbreviations: AUC (0-12 weeks) = area under the curve (0 to 12 weeks).; PK = pharmacokinetic.

Donanemab concentration-time profiles following standard and modified titration regimens overlap completely after Week 12, where the same dosing regimen is used (Figure 34). In the first month with dose-proportional PK (350 to 1400 mg), donanemab serum levels following 350 mg (modified titration regimen) are half of those following standard dosing (700 mg). Nevertheless, C_{trough} and C_{av}, associated with amyloid plaque reduction, were achieved for some of this period even with the lower 350 mg initial dose. For the second inter-dosing period (700 mg for both arms), achieved serum concentrations were overlapping. In the third inter-dosing period, the 1050 mg dose in the modified titration regimen achieved slightly higher C_{max}, C_{av}, and C_{trough} compared with 700 mg in the standard dosing regimen. Exposure metrics were still within the therapeutic range and lower than those achieved with 1400 mg; hence, there were no safety concerns.

Figure 34. Comparison of concentration-time profiles following standard and modified titration regimens



Simulations using the final population PK model (10,000 iterations were carried out). Solid red line: median of predicted concentrations; shaded areas: 90% prediction intervals (includ. between-participant and residual error).

Figure 35. Comparing the amyloid plaque at baseline and Week 24 and 52 from standard (N=206) and modified titration (N=212) dosing using the final population PK/amyloid plaque model

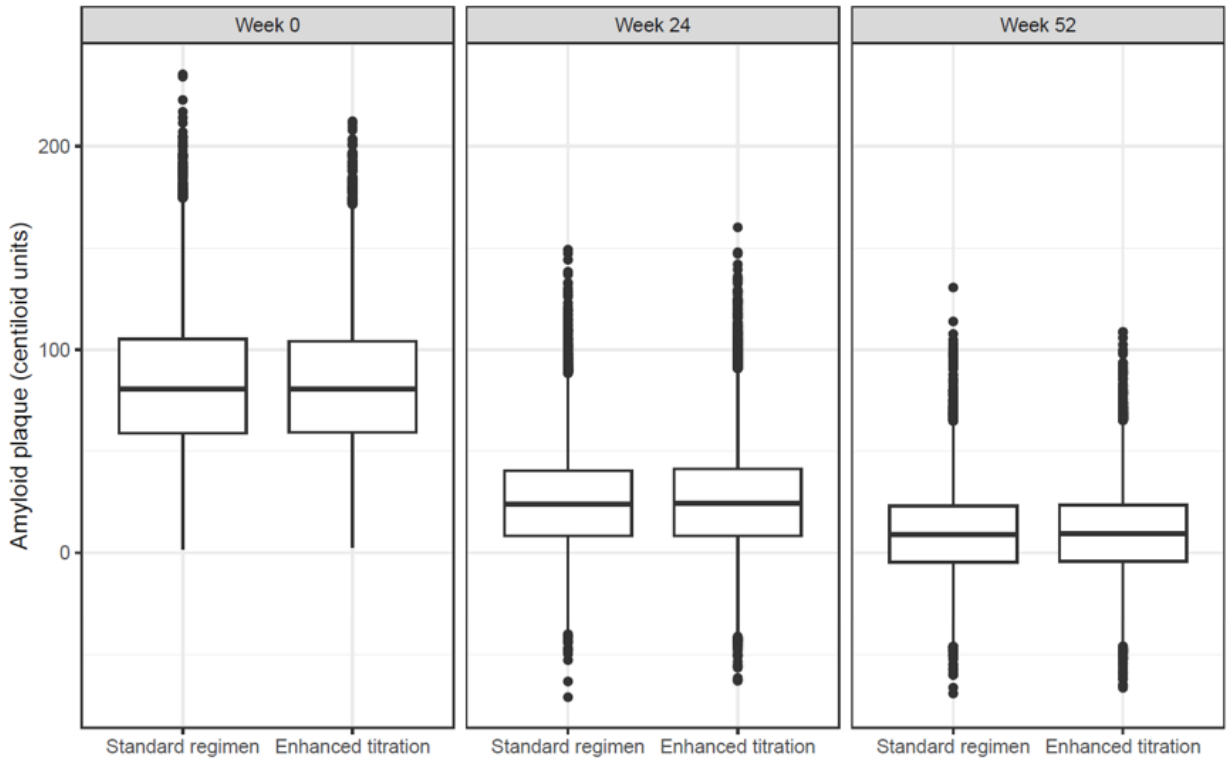
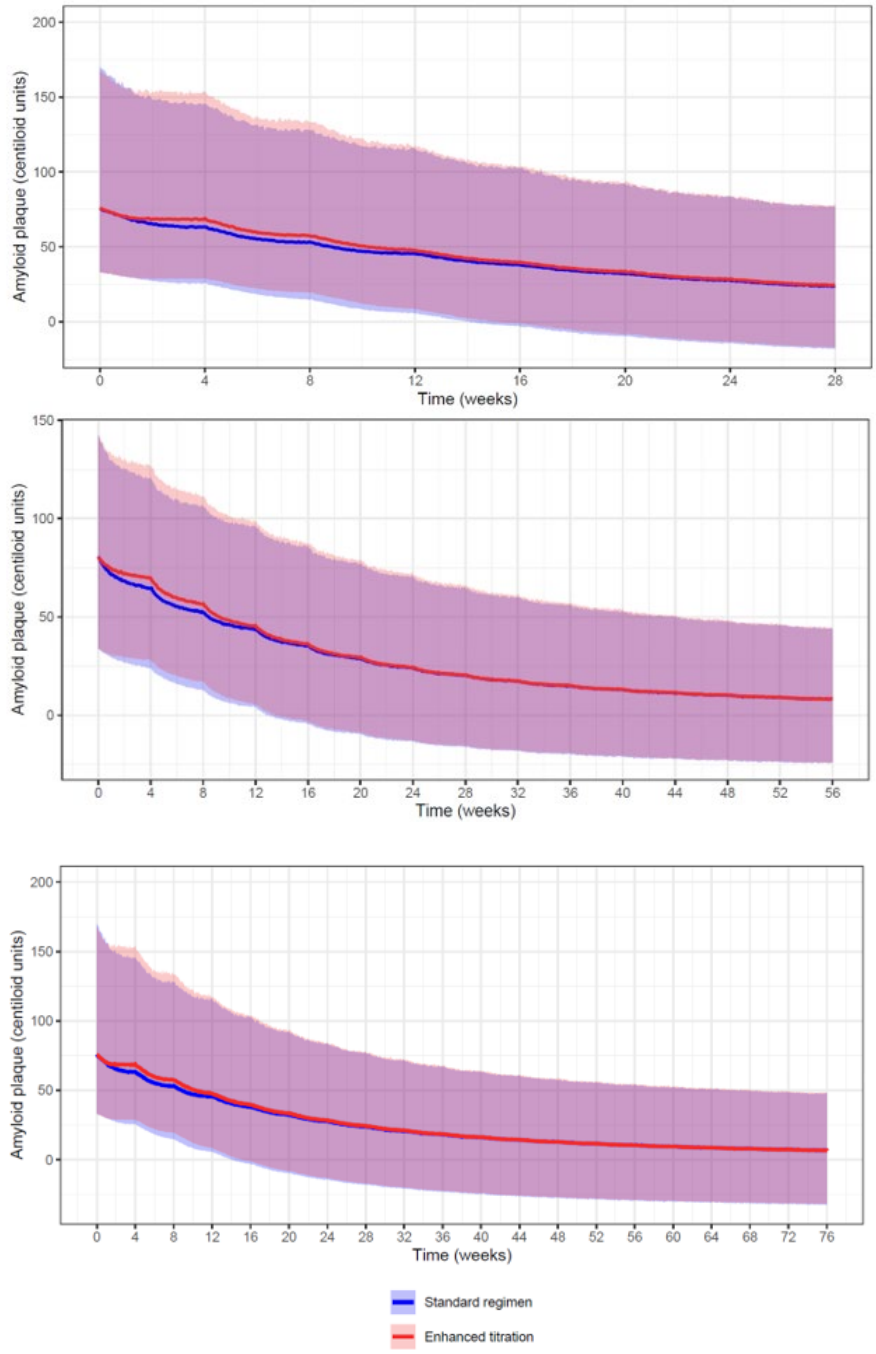


Figure 36. Comparison of amyloid plaque over time following standard and modified titration regimens



Abbreviation: PK = pharmacokinetic. Simulation using the final population PK/amyloid plaque model. Solid red line: median of predicted concentrations; shaded areas: 90% prediction intervals (including between participant and residual error).

In summary, the standard and modified titration dosing regimens in Study AACQ achieve similar cumulative doses and exposures and provide consistent $C_{av,ss}$ associated with amyloid plaque reduction (Figures 35 and 36). Bridging based on exposure for these 2 regimens was ascertained. Based on these results, and in line with EMA guideline (2023) that support model-based approaches as the main

source of evidence to inform approval of alternative posology for monoclonal antibodies, the PK/PD data from modified titration regimen support bridging between the standard and the modified titration.

Summary of ARIA/ICH >1cm Related Fatalities Across the Donanemab Clinical Programme

Seven deaths in donanemab treated patients across the clinical programme (n > 3500) were either causally associated with an ARIA event (n=3), occurred in a participant with prior serious ARIA (n=1), was secondary to a haemorrhagic event after use of a thrombolytic for management of stroke like symptoms in the setting of ARIA-E (n=2), or was confounded by medical history (n=1). Table 62 provides a summary of these fatalities and proposed risk minimisation measures that would potentially avoid such outcomes.

Table 62. Summary of ARIA/ICH > 1cm Related Fatalities Across the Donanemab Development Programme (amended by the assessor – in red)

Fatal Case (Study) Participant Demographic	Relevant Information	Relevant Risk Minimisation
ARIA-H (AACI-PC) 70-80, , APOE ε4 NC	Baseline superficial siderosis (50mm), symptomatic ARIA-E with headache. Donanemab infusion n = 2. Severe ARIA-H; severe cerebral haemorrhage/ haemorrhagic stroke led to death As per the narrative, the patient had baseline risk factors, e.g. hypertension	SmPC: Contraindication for SS and uncontrolled hypertension; MRI prior to 2nd dose. HCP education Additionally: Discontinuation of donanemab in case of radiographically severe ARIA
ARIA-E (AACI-PC) 70-80, , APOE ε4 hetero	ARIA-E was severe and reported as SAE; Symptomatic confusion, agitation and speech abnormalities. Donanemab infusion n = 3.	SmPC: MRI prior to 2nd dose and optional MRI prior to 3rd dose HCP educational material Additionally: Discontinuation of donanemab in case of radiographically severe ARIA
Death (AACI-PC) (prior ARIA-E/H) 70-80, , APOE ε4 hetero	First presentation was severe ARIA-E + 11 microhaemorrhages (visit 5); Multiple episodes of ARIA-E/H on rechallenge. Developed more than 20 microhaemorrhages. during treatment. Symptomatic nausea/vomiting. Donanemab infusion n = 10. As per the narrative, the patient had baseline risk factors, e.g. hypertension, hyperlipidaemia, type 2 diabetes etc. According to the narrative hypertension worsened from Day 24 on.	SmPC: Guidance on permanent discontinuation for recurrent severe ARIA events. Additionally: Discontinuation of donanemab already for the first radiographically severe ARIA event. Contraindication for uncontrolled hypertension. Risk assessment prior to rechallenge. HCP educational material
ARIA-E (AACI-LTE) 70-80, , APOE ε4 hetero	Symptoms of confusion, headache, severe gait disturbance and loss of vision. Donanemab infusion n = 5. ARIA-E identified on MRI Day 694 and treatment with steroids started on Day 699. Delayed treatment with steroids. Patient had hypertension as risk factor.	SmPC: MRI on suspected symptoms. Contraindication for uncontrolled hypertension. HCP educational material
Intracranial Haemorrhage (AACI-LTE) 70-80, , APOE ε4 hetero	Symptoms of ischemic stroke treated with tenecteplase. ARIA on central MRI. Donanemab infusion n = 5.	SmPC: Guidance on thrombolytics HCP educational material Patient Card
Thalamic Haemorrhage (AACI-A9) 70-80, , APOE ε4 hetero	H/o HT, T2DM, hyperlipidaemia, stroke, Parkinson's disease. Thalamic haemorrhage on Day 409. Per neurologist, likely hypertensive haemorrhage. Hypertension as risk factor/ baseline condition.	SmPC: Contraindication for uncontrolled hypertension. HCP educational material
Intracerebral Haemorrhage (AACQ) 70-80, , APOE ε4 hetero	Day 150, mild (R) parietal ARIA-E on MRI. Left hemiparesis and seizure on Day 157, diagnosed (R) MCA stroke by CT. No MRI. Treated with tenecteplase. Donanemab infusion n = 6. Hypertension was reported as medical history	SmPC: Guidance on thrombolytics. Contraindication for uncontrolled hypertension. HCP educational material Patient Card

Abbreviations: CT = computed tomography; HCP = healthcare professional; LTE = long term extension; M = male; MRI = magnetic resonance imaging; T2DM = type 2 diabetes mellitus; SmPC = Summary of Product Characteristics.

General consideration on the donanemab clinical study programme

Compared with other contemporary AD studies, the donanemab programme enrolled an older and more clinically advanced population (by clinical scale/stage assessment, and larger portion with symptomatic AD medication use) with higher pathological disease burden (higher baseline amyloid load) and larger portion of APOE ε4 carriers and homozygotes. These baseline differences are hypothesised to result in a harder-to-treat population, being more susceptible to both drug-related and unrelated AEs or death due to comorbid illness. This is illustrated by the safety profile observed in participants receiving placebo in Study AACI-PC and in another contemporary AD trial (Table 63).

The population in Study AACI differed from those included in other contemporary trials in key aspects, including lower baseline MMSE scores (reflecting greater cognitive impairment), more frequent superficial siderosis, and notably, higher baseline amyloid burden in AACI.

Table 63. Safety profiles in placebo trial patients

	TRAILBLAZER-ALZ 2 Placebo[a,1] N=874 n(%)	**Contemporary AD Trial Placebo[2,3,4] N=897 n(%)**
Overview of AE		
Deaths	10 (1.1)[b]	7 (0.8)
SAEs	138 (15.8)	101 (11.3)
DCAE (Treatment)	38 (4.3)	26 (2.9)
Overview of ARIA		
ARIA-E	18 (2.1)	15 (1.7)
ARIA-H	119 (13.6)	80 (8.9)
Microhaemorrhage	109 (12.5)	68 (7.6)
Superficial siderosis	26 (3.0)	21 (2.3)
Infusion-related reaction	4 (0.5)	66 (7.4)

Abbreviations: AD = Alzheimer's disease; AE = adverse events; ARIA = amyloid-related imaging abnormalities; N = number of participants; SAE = serious adverse event.

[a] Data reported for combined tau population.

[b] Deaths were also included under serious AEs and discontinuations due to AEs.

c Based on MRI

1. Sims JR, et al 2023. 2. van Dyck CH, et al 2023 3. Iwatsubo T. 2022; 4. Honig et al. 2024

Risk Minimisation Measures and Additional Pharmacovigilance Activities

To optimise the benefit-risk of donanemab in the indicated population, the applicant is proposing a comprehensive risk management approach, including precautions not included in clinical trials, relative to the key risk of ARIA. These include routine risk minimisation (labelling guidance and routine surveillance activities), additional risk minimisation activities as well as post authorisation pharmacovigilance studies.

Donanemab's safety profile is consistent with known, class risks for amyloid-targeting therapies. The key risks associated with donanemab are ARIA-E/H and hypersensitivity, including IRR.

Routine risk minimisation measures

Labelling guidance

The proposed labelling for donanemab includes guidance for monitoring and managing ARIA taking into account both the learnings from the extensive donanemab development programme and the well-known key risk factors for ARIA. Key elements include:

- **Restriction of indicated population:** the safety of donanemab is enhanced when restricted to *APOE* ε4 heterozygotes and noncarriers. Patients who are APOE ε4 homozygotes will be excluded given their higher risk of ARIA, especially symptomatic and serious ARIA that are more clinically relevant.
- **Mandatory APOE Testing:** testing for APOE status will be mandatory prior to initiation of donanemab.
- **Contraindications:** contrasting the clinical trials, baseline superficial siderosis, identified as an important ARIA risk factor, is contraindicated in real world practice along with the presence of other MRI findings (i.e., prior ICH >1 cm, more than 4 microhaemorrhages or vasogenic oedema (ARIA-E), suggestive of cerebral amyloid angiopathy, along with severe white matter disease).
- **Monitoring ARIA- MRI Schedule**: The label outlines a schedule for recommended MRI.
    - Baseline MRI within 6 months of treatment initiation to identify any recent development of risk factors. This is followed by
    - MRI prior to the 2nd dose, specifically to identify serious ARIA early in treatment.
    - MRI prior to dose titration and prior to 7th dose are recommended given that majority of the ARIA events occur within the first 6 months (24 weeks).
    - Additional MRI prior to the 3rd dose is recommended for those at higher risk for ARIA (e.g. heterozygotes) to identify early ARIA development before it becomes serious or severe.
    - The proposed label also encourages prescribers to do MRIs at any time during treatment based on clinical judgement or on emergence of suspected symptoms.
- **ARIA Management**: In addition to guidance on continuation or suspension of treatment based on radiographic severity and asymptomatic/symptomatic nature of ARIA, the proposed label also instructs prescribers to reassess risk factors prior to rechallenging donanemab after resolution of ARIA-E or stabilisation of ARIA-H.
- **Dosing Stopping Guidance**: The label also specifically guides prescribers on permanent discontinuation of treatment in cases of ICH> 1cm, clinically serious ARIA and radiographically severe recurrent ARIA.

Post-marketing surveillance

To monitor the nature of reports of suspected ARIA in the post-marketing setting, an ARIA/ macrohaemorrhage-specific questionnaire has been developed to collect additional information on ARIA and ICH > 1cm events in the real-world setting (included in Part VII Annex 4 of the EU RMP).

Additional risk minimisation measures

Additional risk minimisation activities are proposed specifically focused on the risk of ARIA, i.e. the implementation of a controlled access programme (CAP), which includes restricted distribution of donanemab to preselected centres with affiliated prescribers, and educational materials for HCPs (prescribers and radiologists) and patients/ caregivers.

Controlled Access Programme

The applicant proposes a controlled access programme in Europe as an additional risk minimisation activity, ensuring that donanemab is exclusively used when all risk minimisation measures are in place.

The donanemab EU CAP acts as a risk minimisation measure in 2 ways:

- **restricting access** of donanemab to preselected centres with affiliated prescribers who have received the educational materials on donanemab treatment and
- **implementing a central registration system ("EU CAP Registration System")** to assist HCPs in
    - assessing patient eligibility,
    - ensuring HCPs access to the educational materials, and
    - confirming adherence to the materials and distribution of the Patient Card.

This CAP is the only controlled access programme in Europe that restricts amyloid-targeting therapy distribution to preselected centres with multidisciplinary teams (including affiliated prescribers) who

- can assess eligibility for donanemab and have access to a validated method to assess brain amyloid pathology,
- have access to APOE ε4 tests,
- have access to MRI (scheduled and unscheduled scans) to detect and monitor for ARIA, and
- have access to infusions and capabilities to identify and manage IRRs.

The affiliated prescribers within these centres will, prior to a patient receiving donanemab, use a central registration system ("EU CAP Registration System") to

- attest to receiving and understanding the required HCP education guide and prescriber checklist;
- confirm that the (anonymised) patient meets required eligibility criteria per label; and
- verify that the patient has been counselled regarding the risks of donanemab and provided with the Patient Card.

Educational Materials

HCP educational materials

The applicant proposes the use of HCP educational materials as additional risk minimisation measures in the EU RMP including an HCP guide and a prescriber checklist:

- The HCP guide provides prescribers and radiologists information on important safety risks related to the use of donanemab, i.e. ARIA-E (cerebral oedema/ effusion), ARIA-H (cerebral microhaemorrhage and superficial siderosis), and ICH. It also informs HCPs about the

indicated patient population, contraindications, the controlled access programme, and the importance of the patient card, including carrying it at all times and to provide to HCPs in emergency situations.
- Prescriber checklist: includes guidance on initial and subsequent treatment, and recommendations for assessments before and during treatment with donanemab.

Patient Card

The Patient Card is attached to the Patient Information Leaflet and provides ARIA-related information, emergency contact details of the treating physician, and patient details to reinforce the importance of seeking medical advice in a timely manner. It also provides a single source of targeted information in an emergency care setting informing physicians of ARIA differential, thus promoting patient safety.

Post authorisation safety studies

During the original procedure, the applicant proposed three PASS studies to characterise the safety profile of donanemab in routine clinical care, and to evaluate the effectiveness of risk minimisation measures (included in the updated EU RMP):

- A registry-based observational study to characterise safety risks, including ARIA, within cohorts of patients treated with donanemab in the EU (Category 1),
- A secondary database study to characterise safety, drug utilisation, and effectiveness of additional risk minimisation activities in patients treated with donanemab in the EU (Category 1), and
- A healthcare provider survey to assess the effectiveness of the donanemab additional risk minimisation activities in the EU (Category 3).

Registry-based observational study (Category 1 PASS)

The proposed PASS is a registry-based cohort study leveraging observational data from the international CorEvitas ALZ-710 Registry, which forms part of a broader, coordinated effort to assess ARIA through global registry initiatives. The ALZ-710 Registry employs a standardised methodology to collect longitudinal data from patients and their treating healthcare providers during enrolment and follow-up visits conducted within routine clinical practice. This registry was selected based on the breadth and depth of its data collection, including comprehensive information on patient demographics, lifestyle factors, ARIA-related risk factors, detailed medication exposure, laboratory and imaging results (APOE genotype, MRI data), and systematic documentation of comorbidities and adverse events, thereby supporting detailed evaluation and characterisation of ARIA events.

The primary objective of the registry-based study is to describe the incidence and severity of symptomatic ARIA (ARIA-E and ARIA-H) within a cohort of donanemab-treated patients in real-world clinical practice in the EU. The study sample size was calculated based on this outcome. Limited reduction in the variability of the estimate of ARIA incidence is achieved at sample sizes greater than 300. Therefore, the enrolment target for the registry will be 400 participants across at least 3 EU countries to account for a potential dropout rate of up to 25%. Sample size and countries included are subject to feasibility based on donanemab uptake in the EU. Cases of ARIA will be captured by health

care providers and reported to the registry via provider follow-up and adverse event case report forms. Per registry case definitions, diagnosis of an ARIA event will be confirmed by the site health care provider via MRI or CT. Each identified MRI/CT confirmed ARIA event will be reported on the "ARIA" adverse event case report form. The date of onset of ARIA events will be determined as follows:

- Asymptomatic ARIA: The date of onset will be defined as the date of initial diagnosis per the MRI/CT scan.
- Symptomatic ARIA: For a patient presenting with symptoms that lead to imaging and subsequently a confirmed ARIA event, date of onset will be defined as onset of symptoms.

Given the currently proposed indication that includes APOE ε4 heterozygotes and non-carries, outcome analyses for the registry-based observational study will include stratification by APOE ε4 genotype.

This study will further reduce the uncertainties in terms of the incidence and consequences of the adverse reactions.

A study synopsis is provided in Annex 3 of the EU RMP.

International, Practice-based Registry for Alzheimer's Disease and Other Dementias

The applicant is supporting the development of the InRAD and maintains the commitment to supplement the proposed registry-based observational study with data from InRAD, as feasible. InRAD is currently developing registry infrastructure to populate a minimum Alzheimer's disease dataset across a large population of European patients, and is intended to be an independent, sustainable resource beyond Phase 4 PASS to generate evidence that improves dementia care and advances patient outcomes. It is expected that data collected by InRAD will have broader patient capture than the Lilly registry; however, the uptake of the registry by the clinical and scientific community and the completeness of the data source is unknown at this time. The applicant will continue to develop the registry-based observational study and commits to supplementing the registry-based PASS with InRAD data, as feasible, once available.

Secondary database study (Category 1 PASS)

The applicant continues to propose a secondary database study to characterise safety, drug utilisation and effectiveness of additional risk minimisation activities in donanemab-treated patients in the EU. This study will complement the primary data collection registry by providing large-scale longitudinal insights across diverse populations. It will also achieve greater statistical precision for estimates of rare events given the larger patient populations available, whereas registries offer detailed, clinically rich targeted data collection in real time, providing more context around observed events. The safety outcomes under evaluation in this study are serious hypersensitivity events (as defined by hospitalisation, for example, due to anaphylaxis) and intracranial haemorrhage. The study will also describe donanemab drug utilisation and monitor compliance with treatment recommendations before donanemab treatment initiation and during donanemab treatment (effectiveness of additional risk minimisation activities). A study synopsis is provided in Annex 3 of the EU RMP.

Healthcare provider study (Category 3 PASS)

Finally, the applicant continues to commit to a healthcare provider survey to assess the effectiveness of risk minimisation measures. This study will aim to include 200 prescribers and 50 radiologists across at least 3 EU countries. The planned study will assess:

- Prescriber and radiologist understanding of the important safety risks related to the use of donanemab detailed in the HCP educational materials, i.e. information relating to ARIA-E (cerebral oedema/effusion), ARIA-H (cerebral microhaemorrhage and superficial siderosis), and intracranial haemorrhage.
- Prescriber and radiologist self-reported adherence to the risk minimisation practices.
- Prescriber knowledge of the prescriber checklist including guidance on initial and subsequent treatment and recommendation for assessments before and during treatment with donanemab.
- Prescriber distribution of the patient card to patients prescribed donanemab for the first time.
- Prescriber awareness and use of the CAP.

A study synopsis is provided in Annex 3 of the EU RMP.

5.2.1. Assessment of the applicant's responses to the grounds for re-examination (ground #2):

The argumentation of the applicant on clinical safety based on the newly provided analyses with the focus on a restricted patient population, i.e. non-carrier and heterozygous carriers of APOE4 can be summarised as follows:

1. ARIA (ARIA-E and ARIA-H) and ICH > 1 cm have been characterised for donanemab in the main study AACI-PC based on its incidence, radiographic severity, and timing during treatment as well as on its presentation as serious and symptomatic events, and incidences during longer treatment duration in patients treated continuously during AACI-PC and AACI-LTE appear consistent with these presentations.

2. Available post-marketing experience of up to 9 months (from the Lilly Safety System [LSS] Global Database, basically from the US and Japan) support the ARIA safety profile characterised in the clinical programme.

3. A modified titration regimen has been evaluated in study AACQ and is proposed as an additional risk mitigating strategy to further reduce the frequency and severity of ARIA(-E) in the restricted population.

4. The population included in study AACI-PC was – within the target population - rather advanced in the disease and with high amyloid burden, which implies an increased baseline risk for ARIA.

5. The proposed risk minimisation measures for ARIA and ICH > 1 cm are based on identified risk factors and are considered extensive with routine management comprising radiographic and symptomatic events as indicated in the proposed label, healthcare professional guide and checklist, patient card, follow-up questionnaire, as well as additional pharmacovigilance activities, including a controlled access programme restricting distribution of donanemab. Moreover, two category 1 and one category 3 PASS studies to further characterise ARIA-E, -H and also ICH>1 cm, as well as effectiveness of RMMs, and drug utilisation are proposed. These issues are discussed in detail in the following section:

1. ARIA (ARIA-E and ARIA-H) and ICH > 1 cm have been characterised for donanemab in the main study AACI-PC based on its incidence, radiographic severity, and timing during treatment as well as on its presentation as serious and symptomatic events, and incidences during longer treatment duration in patients treated continuously during AACI-PC and AACI-LTE appear consistent with these presentations.

Available literature on anti-amyloid treatment is in support of ARIA-E and ARIA-H mainly being asymptomatic, but sometimes also becoming severe (including seizures) with fatal outcomes being reported. Moreover, ARIA-E typically resolves within 6 months after discontinuation of anti-amyloid treatment, while ARIA-H is at best stabilising and therefore persisting on MRI. In one-fourth of patients, ARIA-E re-occurs after re-initiation of anti-amyloid treatment. While a dose effect appears demonstrated for ARIA-E, this is less clear for ARIA-H. It is well documented that ARIA in APOE4 homozygous carriers is more likely symptomatic and severe (Doran et al., 2024).

The CHMP focuses on the newly proposed patient population for which donanemab seeks approval, i.e. APOE4 non-carriers of and APOE4 heterozygous carriers.

Restricting the overall population in the AACI-PC study to noncarriers and heterozygotes of APOE4 results in a population that accounts for 83% of the overall population, which appears to be a representative number to characterise the risk of ARIA in this subgroup.

Study AACI-PC (Trailblazer-ALZ2)

ARIA-E

Restricting the indication to APOE4 noncarriers and heterozygotes results in a reduced incidence of ARIA-E in the donanemab group as compared to the overall population (20.6% vs. 24%). Of the overall ARIA-E events reported in the proposed indicated population, 73% were asymptomatic and 27% were symptomatic. The highest reduction in the incidence of ARIA-E has been reported for asymptomatic ARIA-E (14.9% in the proposed population vs. 17.9% in the overall population). However, the exclusion of APOE4 homozygotes leads to a relative risk reduction of the already low incidences of symptomatic ARIA-E, SAEs of ARIA-E, and recurrent ARIA-E in a range between 13 and 17%, coinciding with the percentage of homozygote APOE4 carriers excluded.

Similarly, radiographic (and symptomatic) severe ARIA-E events were also found less frequent in the proposed indicated population (radiographically severe ARIA-E occurred in 1.4% in the proposed population vs. 1.6% in the overall population treated with donanemab), while the majority of ARIA-E events reported by radiographic severity in the proposed indicated population were mild to moderate (93%).

The incidence of symptomatic ARIA-E in the proposed indication was reported to be 5.6% (vs. 6.1% in the overall population). The most commonly reported symptoms reported were headache, confusional state, dizziness, nausea, and also seizure. Seizures were reported in N=5 patients. Severe symptomatic ARIA-E in the proposed indicated population (APOE4 noncarriers and heterozygotes) in AACI-PC (Table AACI.8.184 CSR) occurred in 5 patients, and involved, seizures, delirium, bradycardia, acute respiratory failure, movement disorder, hemiplegia, headache, and altered state of consciousness.

Serious ARIA-E events occurred in 9 patients (1.3%) in the proposed indicated population treated with donanemab, all of them being symptomatic. Two of the 9 patients with ARIA-E SAEs (both heterozygote for APOE4) died: in the first patient, ARIA-E occurred after the 3rd dose. No additional risk factors have been reported, and screening MRI was normal. This fatality occurred under an earlier AACI protocol with less frequent MRI monitoring (prior to the 4th and the 7th dose) and might have been prevented with additional MRIs in the first 12 weeks of treatment. The second patient with a fatal SAE of ARIA-E with normal baseline MRI experienced a first severe ARIA-E event after the 3rd dose of donanemab and presence of 11 microhaemorrhages (mild ARIA-H), the latter of which increased in numbers during the next weeks. During this time, donanemab was suspended. After complete resolution of ARIA-E, donanemab was restarted. A recurrent symptomatic ARIA-E event occurred prior to the 11th dose, which was radiographically severe. At the same time, 43 microhaemorrhages were counted (severe ARIA-H). Study drug was again suspended for these events. Symptoms remained (confusional state, balance disorder, nausea and vomiting). The patient died few weeks later with donanemab rated as related to the SAEs resulting in death. This death might have been prevented with recommendation to discontinue treatment in patients with radiographically severe ARIA. This preventive risk minimisation measure to avoid serious or even fatal outcomes concerns up to 8% (based on the reported incidence of severe ARIA-H) of the proposed indicated population, who would need to stop treatment with donanemab in case of severe ARIA.

Time to onset of ARIA-E (in line with other anti-amyloid treatments) in the proposed indicated population was within the first 24 weeks (first 7 infusion), and the majority of SAEs of ARIA-E occurred during the first 12 weeks of treatment initiation. Based on MRIs in the overall population (not analysed for the proposed indicated population!), 98% of the first ARIA-E episodes had complete resolution, with a median time to resolution of 58 days and a mean time to resolution of 72.4 days (reference is made to the CHMP AR of Kisunla). Resolution of symptoms occurred in a majority of patients, while there was no follow-up of unresolved symptoms in 15% of patients with symptomatic ARIA-E hampering assessment of clinical consequences.

4.9% of patients treated with donanemab in the proposed indicated population experienced recurrent ARIA-E (up to 4 episodes). With the responses to the Day 120 LoQ in the original procedure (Day 150 clinical AR, Table 2.14), the applicant provided exact numbers of episodes by genotype for ARIA-E. When applying these numbers to the proposed indicated population, there were 145 patients with a single episode of ARIA-E, 35 patients with 2 episodes, 9 patients with 3 episodes, and 4 patients with 4 episodes.

The proposed risk minimisation measures for recurrent ARIA-E (and ARIA-H) are assessed further below.

ARIA-H

ARIA-H is known to be associated with an increased incidence of ARIA-E (Doran et al., 2024).

In the proposed indicated population, a slight reduction of ARIA-H events in the donanemab group as compared to the overall population was noted (incidences: 27.6% vs. 31.4%), driven by a small reduction in asymptomatic ARIA-H (26.5% vs. 30.2%), while symptomatic ARIA-H remained of overall low incidence (1.1% vs. 1.2%). The exclusion of APOE4 homozygotes did not affect isolated ARIA-H. Concurrent ARIA-H as well as recurrent ARIA-H was slightly reduced in the proposed indicated population (12.7% vs. 16.1% in the overall population and 9.9% vs. 12.7% in the overall population). There were two SAEs of ARIA-H in the proposed indicated population, both resulting in death. One patient had concurrent serious ARIA-E. The other fatality (haemorrhagic stroke and ARIA-H) occurred in a noncarrier, who had a baseline MRI finding of superficial siderosis, which is an exclusion criterion for treatment as per the proposed contraindication. Moreover, patients with AD have been reported to have an increased risk for haemorrhagic stroke per se (over and above the usual vascular risk factors) due to the biological association of AD with cerebral amyloid angiopathy (Waziry et al., 2020).

Regarding radiographic severity, severe ARIA-H was found reduced in the proposed indicated population (incidence of 7.6% in the proposed population vs. 10.4% in the overall population treated with donanemab); the majority of ARIA-H events by radiographic severity were mild to moderate (72%).

9.9% of patients treated with donanemab in the proposed indicated population experienced recurrent ARIA-H (up to 4 episodes). With the responses to the Day 120 LoQ in the original procedure (Day 150 clinical AR, Table 2.14), the applicant provided exact numbers of episodes by genotype for ARIA-H. When applying these numbers to the proposed indicated population, there were 195 patients with a single episode of ARIA-H, 70 patients with 2 episodes, 21 patients with 3 episodes, and 2 patients with 4 episodes in comparison to 268 patients with a single episode of ARIA-H, 109 patients with 2 episodes, 30 patients with 3 episodes, 5 patients with 4 episodes, 3 patients with 5 episodes, and one patient with 6 episodes in the overall population.

Similar to ARIA-E, most of the (first) ARIA-H events occurred within 24 weeks of treatment initiation, while subsequent ARIA-H episodes occurred early in treatment and throughout the study AACI-PC in the overall population (reference is made to the CHMP AR; Figure 13; no data provided for the proposed indicated population). At present, the SmPC recommends conducting mandatory MRIs within 6 months prior to treatment start, prior to the 2nd dose, prior to dose increase, and prior to the 7th dose, and – for patients with high ARIA risk – an additional MRI prior to the 3rd dose. Notwithstanding, any symptoms suggestive of ARIA at any time during treatment should trigger clinical evaluation including an MRI (section 4.2 of the SmPC). Given that isolated ARIA-H can occur at any time (reference is made to the Day 150 clinical AR), vigilance is also needed after the first 24 weeks of treatment; at present, risk minimisation measures do not fully address the occurrence of isolated ARIA-H at any time during longer treatment duration (see section on RMMs below).

ICH > 1 cm

As referenced by Honig et al. (2024), the rate of ICH>1 cm in PBO arms of AD studies ranges from 0.4% – 1%. Intracerebral haemorrhage >1 cm (also referred to as macrohaemorrhage) including haemorrhagic stroke and cerebral haemorrhage was observed in participants treated with either donanemab or placebo. In the proposed indicated population, there were 3 patients (0.4%; all of them being APOE4 heterozygotes) with ICH > 1 cm in the donanemab group and 2 patients in the placebo group (0.3%); thus, the incidence with donanemab remains within the placebo rates from AD trials. However, and similar to isolated ARIA-H, ICH > 1 cm can generally occur at any time during treatment; thus, the proposed MRI monitoring is not fully reassuring of reducing the risk for ICH. As part of the original procedure, 'Macro-haemorrhage' was evaluated by PTs Cerebral haemorrhage and haemorrhagic stroke resulting in more events in donanemab-treated patients than in placebo patients (1.3% vs. 0.8%, resp.; All Dona: 1.3%). Therefore, the proposed SmPC includes intracranial haemorrhage as a common ADR in section 4.8.

Serious events of ICH > 1 cm were reported in two patients in the proposed indicated population (one patient on placebo and one patient treated with donanemab, who was a APOE4 heterozygote). None of the two SAEs was fatal. However, the overall number of SAEs of ICH > 1 cm in AACI-PC is too small to draw firm conclusions. In addition, in study AACI-A9 (the open-label "safety addendum"), one fatal SAE of thalamic haemorrhage was reported in an APOE4 heterozygote patient treated with donanemab for 14 doses. The macrohaemorrhage was not associated with ARIA but rated as related to donanemab. The patient had various cardiovascular risk factors for ICH, e.g. hypertension, type 2 diabetes, hyperlipidaemia, coronary artery disease, tobacco and alcohol usage, and stroke. These risks are well characterised in patients with CAA, which is a major cause of intracerebral haemorrhage (Lioutas et al., 2020; Voigt et al., 2024; Wagner et al., 2021).

Post-treatment safety in patients who discontinued donanemab in study AACI-PC has been evaluated and submitted as part of the Kisunla Day 180 LoQ for the overall population. No new analyses for the proposed indicated population have been presented in the grounds for re-examination. As a result of the evaluation of AEs in the overall population, the occurrence of ARIA during treatment with donanemab in AACI-PC up to 18 months did not impact on the safety post-treatment (i.e. after discontinuation of donanemab), and the incidences of AEs and SAEs were in line with the placebo group in AACI-PC. ARIA events also occurred after discontinuation from donanemab treatment, and the incidence of ARIA-E was low in both groups of patients (with and without ARIA in the AACI-PC period) but slightly higher in patients with previous ARIA. ARIA-E post-treatment was by majority asymptomatic. For ARIA-H, the incidence post-treatment was 2.5-times higher in patients

with previous ARIA as compared to those without ARIA and higher overall as compared to placebo patients in study AACI-PC. The observation time adjusted incidence rate (OAIR) for ARIA-H in donanemab-treated patients post-treatment was 3-times higher in those with previous ARIA as compared to the placebo group in AACI-PC (30.7 vs. 10.4), while the rate for post-treatment ARIA-H was similar for patients without ARIA and the placebo group. Although, it cannot be denied that ARIA can trigger subsequent events, it is also agreed with the applicant that the increased incidence of post-treatment ARIA-H might be due to more frequent MRIs to monitor for stabilisation and therefore detection of events that would have otherwise remained undetected. In addition, it appears plausible that there were more APOE4 carriers among patients with ARIA during AACI-PC and more APOE4 noncarriers among patients without ARIA during AACI-PC, while it remains unclear how many patients with ARIA during AACI-PC with post-treatment safety data concerned the group of patients that is now excluded from the proposed indication (i.e. homozygote APOE4 carriers).

Study AACI-LTE

With regard to the proposed indicated population, N=1247 patients were treated with donanemab in either AACI-PC or its LTE or in both, and 1002 of 1247 patients were specifically treated with donanemab in the LTE. For them, up to 36 months safety data are available.

Comparison of adverse events between patients treated for the first time with donanemab in the LTE (who were previously treated with placebo) and patients, who continued treatment with donanemab from the AACI study in the LTE revealed no increase in the overall AE rates for patients with continued treatment, but lower rates of treatment discontinuations due to AEs and TEAEs related to study drug, which might be a result of less frequent ARIA-E events with continued donanemab treatment.

ARIA-E

The incidences of ARIA-E (overall, asymptomatic, symptomatic, SAEs, and recurrent ARIA-E) for donanemab in study AACI-PC alone versus the combined donanemab treatment periods of studies AACI-PC and AACI-LTE for the proposed indicated population, as well as the radiographic severity of ARIA-E (including symptomatic events) was almost identical. This can be interpreted in a way that incidences of ARIA-E do not worsen over time, being most prominent during treatment initiation. Likewise, radiographical severity during longer treatment remains similar.

One fatal SAE of ARIA-E occurred in a patient treated with placebo in study AACI-PC. The event was symptomatic and detected after the second 1400 mg dosing, while previous MRIs were in line with the baseline MRI showing a single microhaemorrhage. The patient's condition worsened despite corrective (but delayed) corticosteroid treatment. The patient had hypertension as a potential risk factor for ARIA (Zimmer et al. 2025; Sperling et al. 2011).

Onset of ARIA-E as well as recurrence in the LTE study were similar to AACI-PC.

ARIA-H

Patients reflecting the proposed indicated population (APOE4 noncarriers and heterozygotes), who received donanemab during AACI-PC and AACI-LTE were reported to have slightly higher incidence of overall ARIA-H events as compared to the AACI-PC alone (34.2% vs. 27.6%), mainly driven by higher incidences of asymptomatic ARIA-H (33.4% vs. 26.5%). Likewise, there was a higher incidence of isolated ARIA-H (17.3% vs. 12.4%) and recurrent events of ARIA-H (13.1% vs. 9.9%). 38% of patients, who were treated with donanemab in studies AACI-PC and AACI-LTE and reported with ARIA-

H, had more than one episode. The increased incidence is thought to be driven by (1) patients treated with placebo in AACI-PC, who were treated with donanemab for the first time in the LTE, and (2) patients treated continuously with donanemab through study AACI-PC and its LTE, who developed recurrent events. Moreover, isolated ARIA-H can occur at any time during treatment.

No difference was noted for symptomatic ARIA-H and SAEs of ARIA-H that occurred with an overall low incidence in studies AACI-PC and AACI-PC + AACI-LTE combined.

Radiographic severity of ARIA-H in the proposed indicated population for donanemab during AACI-PC and AACI-LTE was found in line with the findings in the AACI-PC, i.e. the majority of ARIA-H events by radiographic severity were mild to moderate (72%). Severe radiographic ARIA-H was less frequent in the proposed indicated population as compared to the overall population (9.3% vs. 12.5%), which includes APOE4 homozygotes (a quarter of patients who were homozygote for APOE4 had severe ARIA-H).

ICH > 1 cm

Four additional events of ICH > 1 cm occurred in the AACI-LTE (one event in a noncarrier and three events in APOE4 heterozygotes). The incidence of ICH > 1 cm was similar in the proposed indicated population and the overall population in the AACI-PC and AACI-LTE analysis (0.6% and 0.7%). One of two ICH > 1 cm events reported as serious was fatal (in an APOE4 heterozygote patient-ID). While death was attributed to acute ischaemic stroke, the patient died from multiple intracranial haemorrhages after receiving tenecteplase. As per the investigator, "*the presenting CVA was not related to the study drug, but the resulting haemorrhages from tenecteplase (reported as tissue plasminogen activator [tPA]) could have been made worse by cerebral amyloid angiopathy and amyloid removed by blinded study drug*". Therefore, a warning is included in section 4.4 with regard to initiation of thrombolytics in patients treated with donanemab and description of ICH as an ADR in section 4.8.

For an analysis of **long-term safety in patients treated with donanemab beyond 18 months** in the LTE, reference is also made to the original procedure (Day 195 clinical Rapp AR, Question 27). Patients receiving donanemab for more than 18 months in the LTE (N=172 patients from the overall population) have been compared to patients with 18 months treatment duration in AACI-PC (N=853 patients).

Based on the results in the overall population, as expected due to their occurrence early during treatment initiation, the observation time-adjusted incidence rate of ARIA-E (including SAEs and symptomatic events) decreased with longer treatment duration. In contrast, the incidence of (asymptomatic) ARIA-H events, as expected due to their occurrence not limited to earlier time points, increased in patients treated with donanemab beyond 18 months in the LTE (50.6% vs. 31.5% in AACI-PC), while at the same time the observation time-adjusted incidence rate slightly decreased. Symptomatic ARIA-H and SAEs decreased both in incidence and OAIR. None of the 172 patients continuously treated with donanemab beyond 18 months reported ICH > 1 cm, and the two deaths reported beyond 18 months were not related to ARIA.

Of note, this analysis has not been updated for the proposed indicated population, which hampers an adequate comparison to the 18 months data in the AACI-PC. Moreover, interpretation needs to be made with caution given the small number of patients with data beyond 18 months.

Supportive data from the Phase 2 study AACG (Trailblazer-ALZ) do not indicate a different safety pattern for ARIA as compared to the placebo-controlled pivotal study and its extension.

Conclusion

In summary, the analyses for AACI-PC focussing on APOE4 noncarriers and heterozygotes imply that the incidences of overall ARIA-E (20.6%) and ARIA-H (27.6%) for donanemab are lower as compared to homozygotes of APOE4 (41.3% and 50.3%, respectively). Moreover, longer treatment duration did not increase the incidences of ARIA-E, serious ARIA-E, and symptomatic ARIA-E, which is in line with the expectations that events mainly occur during the first 24 weeks of treatment. Radiographically, ARIA-E was severe in a minority of patients and the exclusion of homozygous APOE4 carriers further reduces severe ARIA-E, which is expected to lower the risk of potentially serious and life-threatening events, e.g. seizures, ICH, and haemorrhagic stroke. Radiographic severity did not worsen with longer treatment duration.

The exclusion of homozygote APOE4 carriers from the overall population also reduces the incidence of ARIA-H with donanemab, while it remains higher in the proposed indicated population as compared to placebo. However, several studies imply an ARIA-H prevalence between 9.2% and 33% in patients with AD not treated with ATTs (Raman et al., 2014; Yaari et al., 2022). ARIA-H frequently co-occurs with ARIA-E and the incidence of ARIA-H events (but not the radiographic severity) was slightly higher with longer treatment duration; isolated ARIA-H is expected to occur during the entire treatment period with donanemab, which warrants an additional MRI after the first 24 weeks of treatment to be specified in the SmPC (section 4.2).

With regard to occurrence of ICH > 1 cm, the three patients concerned were all APOE4 heterozygotes; therefore, the numbers for the proposed indicated population and the overall population are the same. ICH > 1 cm exclusively in APOE4 heterozygotes in study AACI-PC is considered to be a chance finding given that the incidences of ICH > 1 cm during the LTE were more evenly distributed among genotypes (additional cases in the LTE concerned 1 noncarrier, 3 heterozygotes and 3 homozygotes). The two fatalities subsequent to SAEs of ICH > 1 cm (one in substudy AACI-A9; one in the AACI-LTE) occurred in patients with risk factors (hypertension and thrombolytic treatment), both of which need to be reflected in the product information. Based on the combined AACI-PC and LTE results, the reported incidence of ICH > 1 cm in donanemab-treated patients (0.6%) was found in line with the rate of ICH > 1 cm in placebo arms of AD studies ranging from 0.4% – 1% (Honig et al., 2024).

Based on the aforementioned analyses by genotype and up to 36 months of treatment with donanemab (during AACI-PC and LTE) and exclusion of the patient population with highest risk for adverse outcomes, ARIA events are considered to be sufficiently characterised with regard to incidences, timing, and radiographic severity in the proposed indicated population.

Moreover, the safety related to ARIA and ICH as indicated above in the single studies does not change when compared to the All-Dona analysis set, which includes all available controlled and uncontrolled study data for donanemab (Table 9).

2. Available post-marketing experience of up to 9 months (from the Lilly Safety System [LSS] Global Database, basically from the US and Japan) support the ARIA safety profile characterised in the clinical programme.

As part of the Grounds for re-examination, the applicant provided additional post-marketing safety data demonstrate the applicability of the occurrence of ARIA and ICH and related symptomatology or

clinical outcomes to a real-world patient population. The company's Global Safety Database (GSD) spans over 9 months from IBD on 2 July 2024 to 2 April 2025 and contains data mainly from the US and Japan, where donanemab is indicated for an unrestricted population (i.e. including APOE4 homozygotes). However, exposure to donanemab can only be estimated based on distributed vials so far (52,224 vials). The known limitations of spontaneous reporting need to be considered, including limited detailed information on the perceived cases.

87 of the 202 ARIA events reported post-marketing concerned ARIA-E:

Despite the incomplete information on ARIA cases in the database, it appears that the TTO was in line with the appearance of ARIA-E in the clinical programme, i.e. within the first 2 months of treatment. Radiographic severity was unknown in almost 2/3 of cases but in line with the clinical study data. In a majority of the events with known action, donanemab was either interrupted or withdrawn. When APOE4 status was reported, the majority of events related to APOE4 carriers. A majority of ARIA-E events (with known outcome) were reported as recovered or recovering.

1/3 of the reported ARIA-E events were symptomatic with symptoms in line with the clinical study data (mainly headache and confusion). While only 11 of 87 events were classified as SAEs, the company assigned an additional 56 events as SAEs given that ARIA-E is per se classified as medically important. The SAEs were mainly symptomatic (mostly headache, confusion; but also aphasia/ dysphasia and seizure has been reported). Serious ARIA-E was by majority reported in APOE4 carriers (when genotype was available). One ARIA-E event concurrent with cerebral haemorrhage was fatal lacking further information (see below).

84 of the 202 ARIA events reported post-marketing concerned ARIA-H (microhaemorrhage and superficial siderosis):

Of these, ~40% were reported as concurrent with ARIA-E. TTO implies occurrence within the first 3 months. Radiographic severity was unknown in ~2/3 of cases but in line with the clinical study data for the reported events. In a majority of the events with known action, donanemab was either interrupted or withdrawn. When APOE4 status was reported, the majority of events related to APOE4 carriers. Half of the ARIA-H events (with known outcome) were reported as recovered or recovering or stabilised. 5 events involved patients with antiplatelet treatment and 2 events were reported in patients with anticoagulant treatment. 26% of the reported ARIA-H events were symptomatic with symptoms in line with the clinical study data (mainly headache and gait disturbance/ inability to ambulate), and in a majority concurrent with ARIA-E. While only 6 of 84 events were classified as SAEs (all of them symptomatic, mainly headache but also 1 seizure, and concurrent with ARIA-E), the company assigned an additional 58 events as SAEs given that ARIA-H is per se classified as medically important. The SAEs were mainly symptomatic (mostly headache, confusion; but also aphasia/ dysphasia and seizure has been reported). One fatality was reported following a fall and head injury in a patient with asymptomatic ARIA-H being a noncarrier of APOE4.

31 of the 202 ARIA events reported post-marketing concerned unspecified ARIA:

These cases were found in line with the specified presentations of ARIA-E and -H regarding radiographic severity, symptoms, and action following the events. However, information on these cases is scarce.

24 events of intracerebral haemorrhage were reported post-marketing:

When information was available, the events occurred early during treatment (first 3 months), the action was interruption or withdrawal of donanemab, 2 of 24 events with known genotype occurred in APOE4 carriers, and no report included concomitant antithrombotic treatment. Only for a single event, information on the outcome was available (death in a APOE4 heterozygote). Further evaluation of these events is hampered by the lack of information on the size of the haemorrhages and exact term (mainly reported as 'brain bleed'). Also, symptoms were rarely reported and included confusion, balance problems, headache, flu-like symptoms, migraine, nausea, vertigo, and visual impairment in four of the events. One report included concurrent small stroke with no further information available.

There were three reports of post-marketing fatalities in patients with ARIA or ICH (one APOE4 heterozygote, one noncarrier and one with unknown genotype). One patient presented with stable, asymptomatic, mild ARIA-H after the first dose with subsequent treatment interruption; death occurred after a fall with head injury while treatment was still interrupted. No further information is available. One patient was reported with ARIA-E and ICH after the first dose of donanemab, both of which were serious/ life-threatening. No further information is available. One patient was reported with ICH after the 3rd dose of donanemab, while previous MRIs were negative. No concomitant antithrombotic medication was reported. No additional information is available.

Conclusion

In summary, the post-marketing experience with donanemab is based on the GSD on ARIA events and ICH > 1cm. The GSD covers up to 9 months of exposure to treatment with donanemab. While events from spontaneous reporting from the GSD are afflicted by limited information, the time-to-onset and severity of events, the involvement of APOE4 carriers in these events, the concurrent appearance of ARIA-H with ARIA-E events in a majority of cases, and the symptoms reported are basically in line with the clinical study data. Of note, when action with treatment was reported, a majority of patients interrupted or discontinued donanemab. This is considered to be covered by the recommendations given in the SmPC based on the MRI outcomes in section 4.2 with additional amendments requested by the CHMP regarding discontinuation of treatment. Post-marketing data contribute to the finding that seizures sometimes occur in patients presenting with ARIA and donanemab treatment. Events of ICH have likewise been reported post-marketing, but background information is too scarce to draw meaningful conclusions; three ICH events were fatal (two of which involved ARIA).

3. A modified titration regimen has been evaluated in study AACQ and is proposed as an additional risk mitigating strategy to further reduce the frequency and severity of ARIA(-E) in the restricted population.

Primary focus in Study AACQ was set on the comparisons between the proposed "modified titration regimen" and the "standard dosing regimen". The modified titration regimen has first been proposed by the applicant following the Day 180 LoQ and reference is made to the Day 195 and Day 225 clinical ARs for the 24-week and 52-week data from study AACQ. These data have also been published by Wang et al. (2025). The provided data on the incidence of ARIA in study AACQ refers to 52 weeks of treatment. Results of the 76-week data have been published during this re-examination procedure (Wang et al., 2025b) and are fully consistent with the 52-week data.

The modified titration regimen differed from the standard titration only in the first three doses of donanemab, i.e. instead of three doses of 700 mg, dosing starts with 350 mg, followed by 700 mg as

the second dose and 1050 mg as the third dose. Overall exposure within the titration period of 3 months remained therefore identical to the standard titration. This is further supported by a comparable cumulative exposure (PK) and similar observed brain amyloid plaque reduction (PD) at Week 24 and Week 52 in line with the standard dosing group, which generally allows bridging. Reference is made to the Day 195 and Day 225 clinical ARs.

The presented comparative data focus on the 52-week data in the proposed indicated population

At Week 52 in the proposed indicated population, the modified titration group showed an approximately 28% relative risk reduction of **ARIA-E** compared with the standard dosing group (14.7% in the modified titration group vs. 20.4% in the standard dosing group). No radiographically severe and severe symptomatic ARIA-E occurred in the modified titration arm but in up to 3 patients in the standard arm. Moreover, a relative risk reduction (RRR) of ~35% and ~56% was seen for symptomatic ARIA-E and recurrent ARIA-E in the modified arm as compared to standard dosing, while no difference could be observed for ARIA-E SAEs. The time-to-onset of ARIA-E for both titration regimens was in line with the data from study AACI-PC. While an impact of the modified titration regimen on overall **ARIA-H** events is not readily clear from the provided incidences (24.6% vs. 25.3%, i.e. a ~3% RRR compared to standard titration), this finding can mainly be ascribed to isolated ARIA-H, which does not strictly occur during treatment initiation but during the entire treatment period with amyloid lowering treatments. In contrast, a 30% relative risk reduction is observed with the modified titration scheme as compared to standard titration for ARIA-H concurrent with ARIA-E (incidence: 9.9% vs. 14%). Symptomatic ARIA-H occurred in a single patient in study AACQ (modified titration arm), and none of the ARIA-H events was rated as serious. Some risk reduction could also be hypothesised for recurrent ARIA-H, basically for APOE4 heterozygotes. Likewise, a trend towards reduction in radiographically severe ARIA-H could be observed in the modified titration arm versus the standard arm. The TTO of ARIA-H for both titration regimens was in line with the data from study AACI-PC.

Up to Week 52, there were 2 patients with events of **ICH > 1 cm** in the modified titration group (1%) and one patient in the standard dosing group (0.5%). One of the two patients in the modified titration arm was a noncarrier and the event was asymptomatic. The other patient (APOE4 heterozygote) presented with a SAE of middle cerebral artery stroke (rated as related to donanemab) following mild ARIA-E and 6 new microhaemorrhages after the 6th dose of donanemab. Death occurred following an intraparenchymal haemorrhage after administration of a tissue plasminogen activator (i.v. tenecteplase). Risk minimisation measures in the SmPC include a warning in section 4.4 with regard to initiation of thrombolytics in patients treated with donanemab, pausing donanemab if anticoagulation needs to be commenced, and description of ICH in section 4.8, which is acknowledged.

Although, APOE4 homozygotes are not part of the proposed indicated population, the impact of the modified titration scheme on the reduction of ARIA is noteworthy: the modified titration group showed a 58% relative risk reduction of ARIA-E compared with the standard dosing group (incidence 23.8% in the modified titration group vs. 57.1% in the standard dosing group). For asymptomatic ARIA-H, the RRR was 40% (incidence 28.6% in the modified titration group vs. 47.6% in the standard dosing group), while ARIA-H concurrent with ARIA-E and recurrent ARIA-H were both reduced by 50%.

In summary, based on the proposed indicated population of APOE4 noncarriers and heterozygotes, the modified titration scheme offers an advantage in the reduction of ARIA-E events, with a relative risk

reduction ranging between 26% for asymptomatic ARIA-E and 56% for recurrent ARIA-E events, and also reduces the risk for ARIA-H concurrent with ARIA-E (RRR ~30%). Two potential mechanisms for the advantage of the modified titration have been hypothesised by Wang et al. (2025) and imply (1) slower removal of vascular amyloid due to reduced antibody binding at lower initial doses leading to a reduction in leakiness and inflammation, and (2) a slower increase in donanemab serum concentration resulting in more gradual mobilisation of amyloid via the perivascular spaces, which limits exacerbation of CAA.

However, any conclusion on the advantage of the modified titration regimen over the standard titration regarding the reduction of ARIA also needs to consider that the patient population in study AACQ slightly differed from the one in AACI-PC. Although inclusion criteria - with the exception of Tau PET (not conducted in AACQ) - were comparable, at baseline less patients in AACQ had a disease severity status in line with mild AD as compared to AACI-PC (likewise, more patients in AACQ had mild cognitive impairment as compared to AACI-PC). Similarly, patients in study AACQ appear less cognitively impaired than those in study AACI-PC based on the mean MMSE score (25.14 in AACQ vs. 22.43 in AACI-PC), and their mean baseline amyloid CL was slightly lower as compared to patients in study AACI-PC (84.40 in AACQ vs. 103.49 in AACI-PC). Therefore, it is reasonable to expect that the modified titration regimen might be even more effective in the reduction of ARIA (especially ARIA-E) in a patient population with higher amyloid baseline burden like the one included in study AACI-PC. This notion is additionally supported by the fact that APOE4 homozygotes, who generally exhibit a greater Aβ deposition, had the largest effect regarding the reduction of ARIA-E and also ARIA-H when applying the modified titration scheme in study AACQ.

Conclusion

Taking into account the comparison of exposure (PK) data, the comparison of amyloid reduction, as well as the overall ARIA safety profile in studies AACI-PC and AACQ, the presented data suggest that the modified titration scheme can serve as an additional risk minimisation measure in the proposed indicated population.

4. The population included in study AACI-PC was slightly different as compared to the pivotal study of another drug in class, evidenced by the comparison of baseline characteristics between the respective placebo groups. Patients in AACI-PC appeared to be more advanced in the disease, which implies an increased baseline risk for ARIA.

The applicant argued that the donanemab programme enrolled a clinically advanced population as compared to other contemporary ATT trials. Indeed, there is reasonable evidence that the patient population in study AACI-PC and the patient population of the phase 3 clinical trial of another ATT (lecanemab [Clarity AD]; reference is made to van Dyck et al., 2023) differ when baseline characteristics of patients in both placebo groups are compared. Placebo-treated patients in AACI-PC as compared to Clarity-AD were slightly older (mean age 73 years vs. 71 years), had a higher baseline amyloid burden as per amyloid centiloids (mean 101.6 vs. 75.03), and a higher cognitive impairment as indicated by a lower MMSE score (mean 22.16 vs. 25.6). Likewise, more placebo patients had concomitant AD symptomatic medication in AACI-PC as compared to Clarity-AD (61.4% vs. 53.5%), which supports a higher disease burden in patients treated in AACI-PC. Moreover, as per the exclusion criteria in AACI-PC, patients presenting with 1 area of superficial siderosis were still allowed to enter the study while in the Clarity-AD trial, patients were not allowed to have even on area of SS at baseline (Cummings et al., 2023). Given that baseline superficial siderosis is often seen in the context of CAA, which is a strong

risk factor for developing ARIA during ATT treatment, one might hypothesise that patients in the donanemab study AACI-PC were at a higher risk for ARIA as compared to patients in the Clarity-AD trial. This is further illustrated when the safety profiles of placebo-treated patients in AACI-PC and Clarity-AD are compared with more placebo-treated patients in AACI-PC reported with SAEs, ARIA events (especially ARIA-H), microhaemorrhages and superficial siderosis as compared to placebo-treated patients in the Clarity-AD (van Dyck et al., 2023).

Conclusion

In summary, the incidence of safety findings related to ARIA in the donanemab programme needs to be interpreted in the context of a population at a high risk for anti-amyloid treatment side effects, due to baseline clinical status and amyloid burden.

5. The proposed risk minimisation measures for ARIA and ICH > 1 cm, are based on identified risk factors and are considered extensive with routine management comprising radiographic and symptomatic events as indicated in the proposed label, healthcare professional guide and checklist, patient card, follow-up questionnaire, as well as additional pharmacovigilance activities, including a controlled access programme restricting distribution of donanemab. Moreover, two category 1 and one category 3 PASS studies to further characterise ARIA-E, -H and also ICH>1 cm, as well as effectiveness of RMMs, and drug utilisation are proposed.

The restriction of the indication by exclusion of homozygous APOE4 carriers is the most important risk mitigating strategy to reduce the occurrence of symptomatic, serious and severe ARIA as well as recurrent ARIA events during treatment with donanemab in clinical practice.

ARIA-E, ARIA-H and ICH > 1 cm is considered to be manageable by routine MRI monitoring relative to a baseline MRI as well as with identification of individual risk factors, and respective recommendations, how to handle these patients. Data in the above sections 1. to 4. do not imply that the proposed indicated population is set at an unacceptably high risk for ARIA and ICH with the following RMMs taken into account:

The mandatory APOE testing, the timing of monitoring, the consequences of ARIA and/ or ICH > 1 cm findings on MRI (i.e. dose suspension, discontinuation of treatment), follow-up measures, risk factors for ARIA/ICH, contraindications, etc. are part of the routine risk communication in the SmPC that has been further refined as part of the grounds for re-examination to address the proposed indicated population. The proposed SmPC section 4.2 covers MRI monitoring and frequencies, MRI follow-up, dosing suspension, and discontinuation of treatment. SmPC section 4.3 covers contraindications in addition to the restriction of the indication in SmPC section 4.1. These include - at present - patients with pre-treatment MRI findings in line with CAA, patients with bleeding disorders that are not under adequate control, patients with severe white matter disease, and conditions precluding MRI monitoring. The proposed SmPC section 4.4 includes detailed description of ARIA and its associated symptoms (if symptomatic); monitoring for ARIA (baseline, during and after dose titration, and if symptoms occur); recommendations for interruption of dosing; radiographic findings (severity); APOE4 carrier status and risk of ARIA; other risk factors (CAA); intracerebral haemorrhage; and concomitant antithrombotic treatment.

Monitoring recommendations and warning statements by the applicant are partly in line with the Appropriate Use Recommendations (AUR) for the treatment with donanemab established by the Alzheimer's disease and Related Disorders Therapeutics Work Group to provide HCPs with detailed

information on the safe use in clinical practice (Rabinovici et al., 2025). These AUR are essentially based on the inclusion and exclusion criteria applied in studies AACG and AACI.

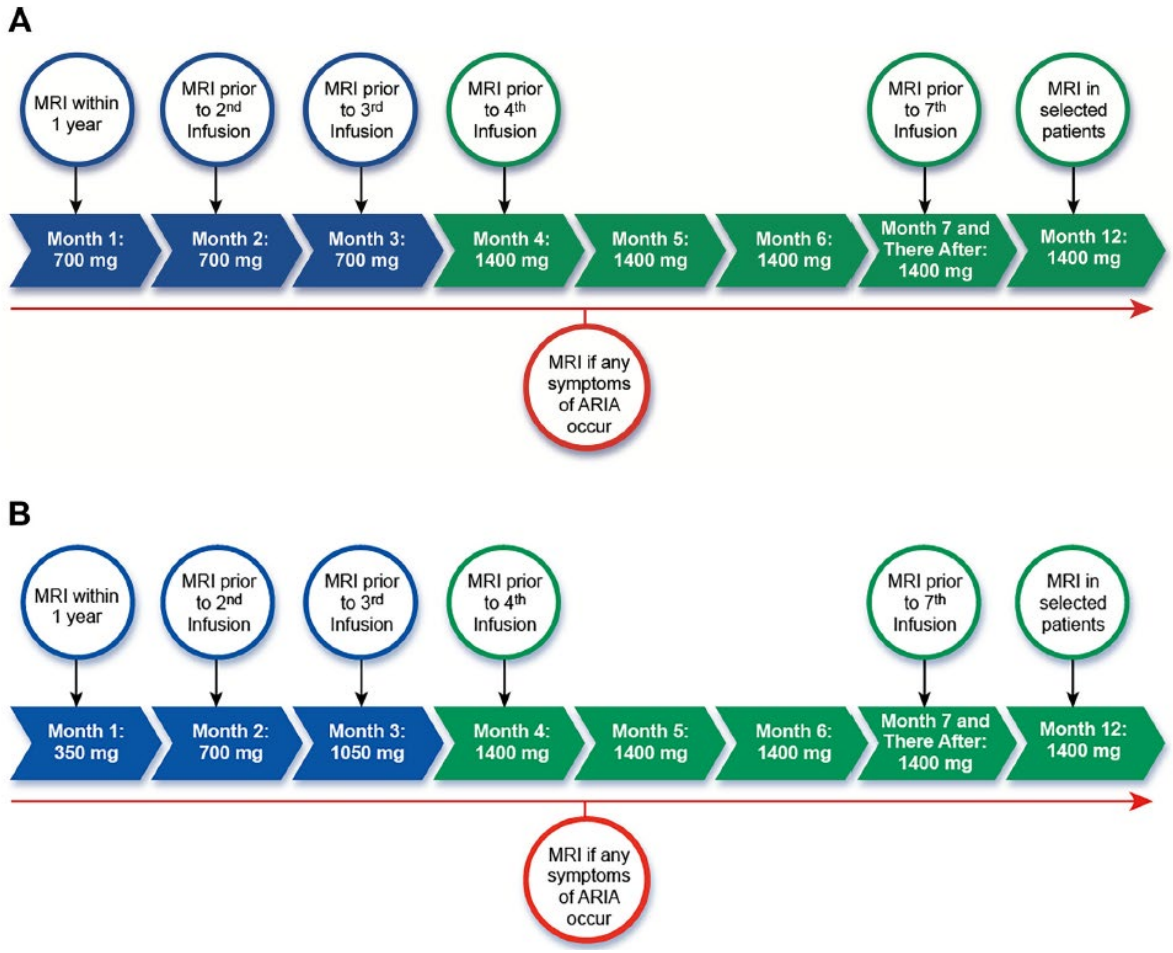
In addition, the CHMP proposed several revisions to the provided SmPC for donanemab in clinical sections based on the assessment above.

Section 4.2 informs on the need for a baseline MRI (within 6 months prior to treatment) as well as for regular MRIs prior to the 2nd dose, prior to dose increase, and prior to the 7th dose. An additional MRI prior to the 3rd dose may allow earlier detection of ARIA in patients with ARIA risk factors. If a patient experiences symptoms suggestive of ARIA at any time during treatment, clinical evaluation should be performed including an MRI (see section 4.4).

An additional MRI prior to the 12th dose (Month 12) should be considered in selected patients (APOE4 carriers and those with evidence of ARIA on previous MRIs, irrespective whether symptomatic or not), which is considered reasonable and also of relevance in the proposed indicated population (Figure 40 below). At the same time, an additional MRI is capable to detect isolated ARIA-H and ICH > 1 cm, both of which can occur at any time during treatment, which means also with longer treatment duration.

The applicant implemented the proposals satisfactorily.

Figure 37. Dose titration and MRI monitoring schedule for donanemab (from Rabinovici et al., 2025)



Based on the radiographic severity and symptomatology of ARIA provided by the applicant for the proposed indicated population (noncarriers and heterozygous carriers of APOE4), the criteria for suspension and discontinuation have been revised during the procedure and are as outlined below.

In case of asymptomatic mild ARIA, dose suspension should be considered based on radiological features of ARIA, number of ARIA episodes and clinical condition.

In case of asymptomatic moderate ARIA and symptomatic mild/moderate ARIA, dose should be suspended until MRI demonstrates radiographic resolution (ARIA-E) or stabilisation (ARIA-H) and symptoms, if present, resolve. A follow-up MRI to assess for resolution (ARIA-E) or stabilization (ARIA-H) should be performed 2 to 4 months after initial identification. Resumption of dosing or permanent discontinuation after ARIA-E resolution and ARIA-H stabilization should be guided by clinical judgment including re-evaluation of risk factors.

In the event of radiographically or symptomatic severe ARIA-E or ARIA-H, treatment with donanemab should be permanently discontinued. Donanemab should also be permanently discontinued after clinically serious ARIA-E, serious ARIA-H, or intracerebral haemorrhage greater than 1 cm.

The instructions above for dosing suspension and treatment discontinuations also take into account the appropriate use recommendations for donanemab by Rabinovici et al. (2025).

Discontinuation of donanemab in the presence of severe asymptomatic or symptomatic ARIA (-E and -H) is considered to further improve ARIA-related safety. This is supported by two fatal events of severe ARIA-H and severe ARIA-E that might have been prevented with early discontinuation of donanemab (Table 26). Based on the AACI-PC data, this preventive risk minimisation measure to avoid serious or even fatal outcomes implies a permanent stop of treatment, that concerns up to 8% of the proposed indicated population treated with donanemab (based on the incidence of severe ARIA-H in study AACI-PC).

Although not being mentioned by the applicant as an additional risk minimisation measure in section 4.2 of the SmPC, the modified titration regimen assessed under 4. is considered to further reduce the incidence of ARIA, especially ARIA-E, but also ARIA-H concurrent with ARIA-E. Given that the modified titration group in study AACQ demonstrated comparable cumulative exposure and similar brain amyloid plaque reduction at Week 24 and Week 52 in line with the standard dosing group, efficacy data can be waived. Moreover, although data with an overall duration of 76-weeks are not yet publicly available, the 24-week and 52-week data in study AACQ are sufficient to describe the ARIA (especially ARIA-E) profile due to early occurrence during treatment with donanemab. Therefore, the modified titration regimen should be considered as an additional risk minimisation measure during this re-examination procedure.

With regard to the observed fatalities related to ARIA and/ or ICH in the proposed indicated population, risk minimisation measures have been proposed by the applicant to preclude treatment with donanemab in patients with the following conditions (SmPC section 4.3):

- patients with baseline MRI findings suggestive of Cerebral Amyloid Angiopathy (CAA), defined as e.g. >4 microhaemorrhages, superficial siderosis or vasogenic oedema (ARIA-E) on pre-treatment MRI,
- patients with bleeding disorders that are not under adequate control,
- patients with severe white matter disease, and
- conditions that preclude MRI monitoring.

Conclusion

While the contraindications proposed above are thought to further reduce the risk of fatal ARIA and ICH with donanemab, the additional following criteria- supported by recommendations of other approved ATTs and available literature data (Rabinovici et al., 2025; Zimmer et al., 2025) – have also been discussed and added to the final section 4.3 of the SmPC:

-Initiation in patients receiving ongoing anticoagulant therapy: in study AACI-PC (as indicated in the AACI-PC CSR), ~10% of patients on donanemab received concomitant anticoagulant treatment at baseline. As per the assessment of the responses to the Day 120 LoQ, the CHMPconcluded that the effect of antithrombotic medication (including aspirin, non-aspirin antiplatelets, and anticoagulants) on ARIA-H and macrohaemorrhage severity did not reveal a clear pattern different than that observed for antithrombotics overall, although numbers were small. However, there is a plausible risk for worsening of ARIA-H and ICH with anticoagulant treatment, which is also reflected as contraindication in the

product information of other ATT products. This is in line with the recommendations by Rabinovici et al. (2025).

-patients with poorly controlled hypertension: 5 of the 7 patients with fatal ARIA/ ICH had hypertension as a risk factor (see Table 21), which legitimates the inclusion of poorly controlled hypertension as a contraindication. This is in line with the findings of Zimmer et al. (2025) (ARIA-E risk increased with higher categories of mean arterial pressure [≥107 mm Hg vs <93 mm Hg]: OR, 1.73; 95%CI, 1.21-2.48; P = .003).

Risk factors for ARIA and the occurrence of intracerebral haemorrhage have been detailed in section 4.4 of the SmPC, including APOE4 carrier status, other risk factors for ARIA (i.e. baseline conditions that are in line with CAA), and concomitant antithrombotic treatment. Restructuring and some revision is proposed to align this paragraph with the recommendations made in section 4.3, and the recommendations provided with other amyloid-targeting therapies and appropriate use recommendations (reference is made to the attached document).

In addition to the routine measures delineated in the donanemab product information, a questionnaire aiming at further characterisation of ARIA and macrohaemorrhage post-marketing has been included in the RMP.

Additional risk minimisation measures have been proposed by the applicant, including a European controlled access programme (CAP), in line with other ATT products, as well as educational materials for HCPs and patients:

- The proposed Controlled Access Programme will ensure that the medicine is exclusively used in preselected centres by trained prescribers and solely when all the RMMs are in place.
- HCP Educational Materials: The ARIA Healthcare Professional Guide aims at distribution to physicians and radiologists prior to prescription of donanemab. The HPC Guide and Checklist reinforces the measures delineated in the SmPC and includes the need for handing out the PIL and patient card to the patient, clarifying information on ARIA and ICH, i.e. identification, symptoms, management and risks (e.g. due to concomitant antithrombotics), and a list of tests to be conducted prior to prescription.
- The patient card includes for example detailed information on ARIA and its symptoms, and importance to seek medical advice for signs and symptoms of ARIA.

In addition, three PASS studies have been proposed, two of which are key to the benefit-risk of donanemab (PASS cat. 1): (1) a registry-based observational study to characterise safety risks, including ARIA, within cohorts of patients treated with donanemab in the EU (Category 1), (2) a secondary database study to characterise safety, drug utilisation, and effectiveness of additional risk minimisation activities in patients treated with donanemab in the EU (Category 1), and (3) a healthcare provider survey to assess the effectiveness of the donanemab additional risk minimisation activities in the EU (Category 3).

In summary, the proposed pharmacovigilance activities as well as the post-marketing measures are considered extensive and appropriate to address the risk of ARIA and ICH with donanemab treatment following the exclusion of APOE4 homozygotes, the patient population at highest risk for severe and serious outcomes.

Summary of the conclusions

Overall, the re-examination CHMP considers that donanemab (Kisunla) is approvable from a clinical safety perspective based on:

-the data from the pivotal AACI-PC study, supported by the available post-treatment safety data in patients who discontinued donanemab during AACI-PC, and the long-term safety data evaluation in the extension study AACI-LTE;
-the proposed indicated population (only APOE4 noncarriers and heterozygotes),
-the proposed extensive routine and additional risk minimisation measures, including a CAP, educational materials, as well as three PASS studies (2 of which are category 1 studies being key to the benefit/risk of donanemab), and
-the supportive data from study AACQ, aiming at a modified scheme for a more gradual titration for the first three doses of donanemab in order to additionally reduce ARIA events (especially ARIA-E).
By exclusion of the homozygous APOE4 population from treatment with donanemab, the CHMP considers that ARIA and ICH > 1 cm is manageable by the proposed risk minimisation measures in the now proposed indicated population if relevant inclusion and exclusion criteria from the phase 3 study AACI-PC are adhered to as indicated in the revised SmPC document.

5.3. Risk Management Plan

5.3.1. Safety concerns

Table 64. Summary of safety concerns (SVIII.1)

Summary of Safety Concerns	
Important identified risks	ARIA-E (cerebral oedema/effusion) ARIA-H (cerebral microhaemorrhage and superficial siderosis) Hypersensitivity events (including IRR)
Important potential risks	Intracranial haemorrhage[a]
Missing information	None

Abbreviations: ARIA-E (cerebral oedema/effusion) = amyloid-related imaging abnormality–oedema/effusions; ARIA-H (cerebral microhaemorrhage and superficial siderosis) = ARIA–haemorrhage/hemosiderin deposition; IRR = infusion-related reaction.

[a] Intracranial haemorrhage includes subdural haemorrhage, subdural haematoma, subarachnoid haemorrhage, cerebral haemorrhage, cerebral haematoma, haemorrhagic stroke, extradural haematoma, haemorrhage intracranial, intraventricular haemorrhage, thalamus haemorrhage, macro-haemorrhage, and cerebrovascular accident.

5.3.2. Pharmacovigilance plan

Table 65. Ongoing and planned additional pharmacovigilance activities (Part III.1)

Study **Status**	**Summary of Objectives**	**Safety Concerns Addressed**	**Milestones**	**Due Dates**
Category 1 – Imposed mandatory additional pharmacovigilance activities that are conditions of the marketing authorisation				
Secondary database study to characterise safety, drug utilisation, and effectiveness of additional risk minimisation activities in donanemab-treated patients in the EU. Planned	The objectives of this observational study, which will be conducted in donanemab-treated patients in routine clinical practice in the EU, are to describe • the incidence of serious hypersensitivity reactions and intracranial haemorrhage[a] • drug utilisation (including, use by patients with Down syndrome and users of antithrombotic or thrombolytic medications), and • the effectiveness of additional risk minimisation activities.	• Hypersensitivity events (including IRR) • Intracranial haemorrhage	Protocol submission Study progress reports Final study report submission	Within 6 months of EU regulatory approval To be provided with the PSUR/PBRER 31 December 2030
Registry-based observational study to characterise ARIA within a cohort of donanemab-treated patients in the EU Planned	The objectives of this study are to describe • the incidence of symptomatic ARIA (ARIA-E and ARIA-H), asymptomatic ARIA, hypersensitivity events, and intracranial haemorrhage[a] within a cohort of donanemab-treated patients in routine clinical practice in the EU • long-term cognitive outcomes and disease progression of patients with ARIA to assess whether these events are associated with accelerated cognitive decline or changes in the rate of disease progression, and	• ARIA-E (cerebral oedema/effusion) • ARIA-H (cerebral microhaemorrhage and superficial siderosis) • Hypersensitivity events (including IRR) • Intracranial haemorrhage	Protocol submission Study progress reports Final study report submission	Within 6 months of EU regulatory approval To be provided with the PSUR/PBRER 31 December 2031

Study Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
	• intracranial haemorrhage within the subgroup of patients receiving concomitant anti-thrombotic or thrombolytic medications.			
Category 2 – Imposed mandatory additional pharmacovigilance activities that are specific obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
None				
Category 3 – Required additional pharmacovigilance activities				
Healthcare provider survey to assess the effectiveness of the donanemab additional risk minimisation activities in the EU Planned	The objectives of the survey are to assess • prescriber and radiologist understanding of the important safety risks related to the use of donanemab detailed in the HCP educational materials, that is, information relating to ARIA-E (cerebral oedema/effusion), ARIA-H (cerebral microhaemorrhage and superficial siderosis), and intracranial haemorrhage, • prescriber and radiologist self-reported adherence to the risk minimisation practices. • prescriber knowledge of the prescriber checklist, including guidance on initial and subsequent treatment and recommendation for assessments before and during treatment with donanemab, • prescriber distribution of the patient card to patients prescribed donanemab for the first time, and • prescriber awareness and use of the CAP.	• ARIA-E (cerebral oedema/effusion) • ARIA-H (cerebral microhaemorrhage and superficial siderosis) • Intracranial haemorrhage	Protocol Submission Final study report submission	Within 6 months of EU regulatory approval Anticipated 31 December 2030

Abbreviations: AD = Alzheimer's disease; ARIA = amyloid-related imaging abnormality; ARIA-E (cerebral oedema/effusion) = ARIA– oedema/effusions; ARIA-H (cerebral microhaemorrhage and superficial siderosis) = ARIA–haemorrhage/hemosiderin deposition; CAP = controlled access programme; EU = European Union; IRRs = infusion-related reactions; PBRER = periodic risk-benefit evaluation report; PSUR = periodic safety update report.

[a] Intracranial haemorrhage includes subdural haemorrhage, subdural haematoma, subarachnoid haemorrhage, cerebral haemorrhage, cerebral haematoma, haemorrhagic stroke, extradural haematoma, haemorrhage intracranial, intraventricular haemorrhage, thalamus haemorrhage, macrohaemorrhage, and cerebrovascular accident.

5.3.3. Risk minimisation measures

Table 66. Summary table of pharmacovigilance activities and risk minimisation activities by safety concern (Part V.3.)

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
ARIA-E (cerebral oedema/effusion)	Routine risk minimisation measures: SmPC Sections 4.1, 4.2, 4.3, 4.4, 4.8, and Section 2 and 4 of the PIL. • Indication statement restricted to ApoE ε4 heterozygotes or non-carriers • Recommendations for monitoring and management of ARIA-E, including symptomatic cases, are included in SmPC Sections 4.2, 4.4, and Section 2 of the PIL. • Testing for ApoE ε4 status should be performed prior to initiation of treatment with donanemab to inform the risk of developing ARIA. • Permanent discontinuation of donanemab treatment after serious ARIA-E, recurrent symptomatic or radiographically moderate or severe ARIA events is included in SmPC Sections 4.2 and 4.4. • Contraindications for use in cases of baseline imaging findings suggestive of increased risk for ARIA or intracerebral haemorrhage,	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Follow-up form for ARIA and intracranial haemorrhage. Additional pharmacovigilance activities: Observational studies: • Registry-based observational study to characterise ARIA within a cohort of donanemab-treated patients in the EU. • Healthcare provider survey to assess the effectiveness of the donanemab additional risk minimisation activities in the EU.

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
	ongoing treatment with anticoagulants, bleeding disorders that are not under adequate control, and poorly controlled hypertension are included in SmPC Section 4.3 and Section 2 of the PIL. Legal Status: Restricted medical prescription Additional risk minimisation measures: • HCP educational material, including prescriber checklist • Patient Card • Controlled access programme	
ARIA-H (cerebral microhaemorrhage and superficial siderosis)	Routine risk minimisation measures: SmPC Sections 4.1, 4.2, 4.3, 4.4, 4.5, 4.8, and Section 2 and 4 of the PIL • Indication statement restricted to ApoE ε4 heterozygotes or non-carriers • Recommendations for monitoring and management of ARIA-H, including symptomatic cases, are included in SmPC Sections 4.2, 4.4, and Section 2 of the PIL. • Testing for ApoE ε4 status should be performed prior to initiation of treatment with donanemab to inform the risk of developing ARIA. • Permanent discontinuation of donanemab treatment after serious ARIA-H, recurrent symptomatic or radiographically moderate or severe ARIA events is included in SmPC Sections 4.2 and 4.4. • Contraindications for use in	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Follow-up form for ARIA and intracranial haemorrhage. Additional pharmacovigilance activities: Observational studies: • Registry-based observational study to characterise ARIA within a cohort of donanemab-treated patients in the EU. • Healthcare provider survey to assess the effectiveness of the donanemab additional risk minimisation activities in the EU.

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
	cases of baseline imaging findings suggestive of increased risk for ARIA or intracerebral haemorrhage, ongoing treatment with anticoagulants, bleeding disorders that are not under adequate control, and poorly controlled hypertension are included in SmPC Section 4.3, and Section 2 of the PIL. • Cautionary language on concomitant use of donanemab with antithrombotic medication, including anticoagulants and thrombolytics, is included in SmPC sections 4.4 and 4.5, and Section 2 of the PIL. Legal Status: Restricted medical prescription Additional risk minimisation measures: • HCP educational material, including prescriber checklist • Patient Card • Controlled access programme	
Hypersensitivity events (including IRR)	Routine risk minimisation measures: SmPC Sections 4.3, 4.4, 4.8 and, Sections 2 and 4 of the PIL • Contraindication for use in patients with prior history of hypersensitivity to donanemab is included in SmPC Section 4.3, and Section 2 of the PIL. • Recommendations for management of serious infusion-related reactions are included in SmPC Sections 4.3, 4.4, 4.8, and Sections 2 and 4 of the PIL.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: Observational studies: • Secondary database study to characterise the safety, drug utilisation, and effectiveness of additional risk minimisation activities in donanemab-treated patients in the EU. • Registry-based observational study to characterise ARIA within a cohort of donanemab-treated patients in the EU.

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
	Legal Status: Restricted medical prescription Additional risk minimisation measures: • Controlled access programme	
Intracranial haemorrhage	Routine risk minimisation measures: SmPC Sections 4.2, 4.3, 4.4, 4.5, 4.8, and Section 2 of the PIL. • Testing for ApoE ε4 status should be performed prior to initiation of treatment with donanemab to inform the risk of developing ARIA. • Contraindications for use in cases of baseline imaging findings suggestive of increased risk for ARIA or intracerebral haemorrhage, ongoing treatment with anticoagulants, bleeding disorders that are not under adequate control, and poorly controlled hypertension are included in SmPC Section 4.3, and Section 2 of the PIL. • Permanent discontinuation of donanemab on identification of intracerebral haemorrhage greater than 1 cm is included in SmPC Sections 4.2 and 4.4. • Cautionary language on concomitant use of donanemab with antithrombotic medication, including anticoagulants and thrombolytics, included in SmPC Sections 4.4, 4.5, and Section 2 of the PIL. Legal Status: Restricted medical prescription	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Follow-up form for ARIA and intracranial haemorrhage. Additional pharmacovigilance activities: Observational studies: • Secondary database study to characterise the safety, drug utilisation, and effectiveness of additional risk minimisation activities in donanemab-treated patients in the EU. • Registry-based observational study to characterise ARIA within a cohort of donanemab-treated patients in the EU. • Healthcare provider survey to assess the effectiveness of the donanemab additional risk minimisation activities in the EU.

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
	Additional risk minimisation measures: • HCP educational material, including prescriber checklist. • Patient card • Controlled access programme	

Abbreviations: ARIA = amyloid-related imaging abnormality; ARIA-E (cerebral oedema/effusions) =ARIA–oedema/effusions; ARIA- H (cerebral microhaemorrhage and superficial siderosis) = ARIA–microhaemorrhage/hemosiderin deposition; EU = European Union; PIL = patient information leaflet; SmPC = summary of product characteristics.

5.3.4. Conclusion

The CHMP considers that the risk management plan version 0.9 is acceptable.

5.4. Pharmacovigilance

5.4.1. Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

5.4.2. Periodic safety update reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant did request alignment of the PSUR cycle with the international birth date (IBD). The IBD is 02.07.2024. The new EURD list entry will therefore use the IBD to determine the forthcoming Data Lock Points.

5.5. Product information

5.5.1. User Consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

5.5.2. Quick Response (QR) code

N/A

5.5.3. Labelling exemptions

A request to omit certain particulars from the labelling as per Art.63.3 of Directive 2001/83/EC has been submitted by the applicant and has been found acceptable by the QRD Group for the following reasons:

Although the size of the vial (20ml) is above the 10ml threshold to qualify for the minimum particulars, the QRD Group considered that an exemption to use the minimum EU labelling requirements for small containers can be granted. Use of full particulars would have a significant impact on the readability of the tri-lingual label, since it would result in a significant reduction of the font size.

5.6. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Kisunla is included in the additional monitoring list since it contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU.

Therefore, the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

6. Updated benefit-risk balance

6.1. Therapeutic Context

6.1.1. Disease or condition

The final agreed indication is:

Donanemab is indicated for the treatment of adult patients with a clinical diagnosis of mild cognitive impairment and mild dementia due to Alzheimer's disease (Early symptomatic Alzheimer's disease) who are apolipoprotein E ε4 (ApoE ε4) heterozygotes or non-carriers with confirmed amyloid pathology (see section 4.4).

Alzheimer's disease is a neurodegenerative disease and the cause of 60–70% of cases of dementia. It is characterised by cognitive and functional decline and is ultimately fatal.

As of 2020, there were approximately 50 million people worldwide affected by Alzheimer's disease.

6.1.2. Available therapies and unmet medical need

Available therapies include cholinesterase inhibitors (donepezil, galantamine, and rivastigmine) for the treatment of mild to moderate Alzheimer's disease, and memantine for moderate to severe Alzheimer's disease. Both therapies are considered symptomatic treatments and are not expected to have disease modifying effects.

Lecanemab (Leqembi) is the first amyloid-targeting therapy authorised in the EU (EC decision granted on 15/04/2025). Lecanemab targets amyloid protofibrils in the brain and may slow the progression of the disease.

There remains a need for effective disease modifying and curative therapies.

6.1.3. Main clinical studies

The single pivotal study of the MAA is phase 3 study AACI is a randomised double-blind placebo-controlled parallel group study with a duration of 76 weeks in 1736 randomised patients.

The patients were included according to reported gradual and progressive change in memory function (>6 months) reported by the patient or informant, an MMSE-score (20-28), and evidence of tau and amyloid deposition (as imaged by PET-scans). Based on their tau deposition patients were divided into the intermediate tau population (patients with low–medium tau pathology) or overall population (also the patients with high tau pathology). At week 24, 52 and 75 donanemab treated patients had a blind switch to placebo if amyloid reduction (on PET scan) was below a certain cut-off point. Data from the long-term extension of Study AACI were also submitted.

Phase 2 study AACG was a randomised, double-blind, placebo-controlled study in 272 patients with MCI due to AD and mild AD with an intermediate tau load. Overall, the design was comparable with study AACI, except that the donanemab dose could be reduced to 700mg or placebo at week 24 or 52.

Study AACQ was a multicentre, randomised, double-blind, Phase 3b study in 842 participants investigating the effect of multiple donanemab dosing regimens (standard vs. dose skipping vs. enhanced titration vs. C_{max}) on ARIA-E and amyloid lowering in adults with early symptomatic AD. The results from this study have been recently published (Wang et al., July 2025b).

6.2. Favourable effects

The benefit-risk conclusions are based on effect estimates from the ITT analysis set of the pivotal study, and on the hybrid reference-based imputation approach (i.e. jump to reference for missing data due to death or severe, symptomatic, or serious ARIA, and copy increments in reference for other reasons).

Primary endpoint - iADRS

The mean difference in change from baseline in iADRS at week 76 between donanemab and placebo in the new target population is **2.65** (95%CI: 1.04, 4.26).

This was also presented as a 19.6**% slowing** of iADRS deterioration.

Key secondary endpoint – CDR-SB

The mean difference in change from baseline at week 76 between donanemab and placebo in the new target population is **-0.69** (95%CI: -0.95, -0.43).

This was also presented as a **28.5% slowing** of CDR-SB deterioration.

Additional secondary endpoints

ADAS-Cog13

The mean difference in change from baseline at week 76 between donanemab and placebo in the new target population is **-1.35** (95%CI: -2.19, -0.51).

This was also presented as a **19.3% slowing** of ADAS-Cog13 deterioration.

ADCS-iADL

The mean difference in change from baseline at week 76 between donanemab and placebo in the new target population is **1.46** (95%CI: 0.50, 2.42).

This was also presented as a **23% slowing** of ADCS-iADL deterioration.

MMSE

The mean difference in change from baseline at week 76 between donanemab and placebo in the new target population is **0.40** (95%CI: -0.015,0.808).

This was also presented as a **13.2% slowing** of MMSE deterioration.

Responder analyses

For responder analyses, patients were evaluated every 3 months for changes during the trial. To be considered progressing to the next stage of disease, a patient had to have 2 consecutive scores greater than their own baseline. Significantly more placebo patients worsened to the next stage of the disease compared to donanemab treated patients, corresponding to a 38% lower risk of progressing to a worse stage of CDR-G with donanemab treatment in the heterozygotes and noncarriers (HR:0.62; p<0.0001)

Long term data and time saved analyses

Long-term extrapolation trajectories from a model assuming fading accumulated time savings estimates the delays to severe dementia (estimated time to CDR-SB = 16) as 26.1 months (25th percentile), 10.8 months (50th percentile), and 5.5 months (75 percentile).

TRAILBLAZER-ALZ 6 (Study AACQ)

The modified dosing regimen showed similar PK/PD to the standard dosing regimen. In particular, participants in the modified titration dosing regimen and standard arms had a similar amyloid reduction from baseline as assessed by PET scans (adjusted mean change at 76 weeks: 70.9 CL versus 72.1 CL, respectively). Participants in the modified titration and standard arms also had a similar P-tau217 response.

The modified titration regimen evaluated in study AACQ was found to further reduce ARIA-E events in the proposed indicated population, while the incidence of overall ARIA-H events remains unchanged despite a reduction in the risk for ARIA-H concurrent with ARIA-E. This finding can mainly be ascribed to isolated ARIA-H, which does not strictly occur during treatment initiation. The currently available data in study AACQ refers to 52 weeks of treatment while data up to 76 weeks of treatment have been collected, which are now publicly available (Wang et al., 2025b), and which are in full support of the 24-weeks data presented in the CHMP AR and the 52-weeks data in this report. Therefore, the modified titration regimen was implemented as an additional measure to reduce the risks and it replaces the previously proposed titration scheme in SmPC section 4.2.

Considerations on the demonstration of efficacy

Statistically significant differences between donanemab and placebo have been demonstrated and is robust to deviations from the assumptions made by the primary estimator. A better approximation of the actual effect size has been achieved – and is presented above - by using different imputation methods depending on the type of missing data. A more conservative approach, such as J2R seems more appropriate for missing data due to ARIA or death, while CIR could be adequate as imputation strategy for other reasons of missing data.

6.3. Uncertainties and limitations about favourable effects

Several of the methods used to assess clinical relevance (such as the establishment of and comparison with MCID values on the continuous scales, the extrapolation to longer-term outcomes by simulation or by comparison with external cohorts) rely on assumptions that cannot – at present – be verified.

Furthermore, for all analyses, the statistical uncertainty regarding the effect estimate should be acknowledged. In particular, looking at confidence intervals for the % slowing estimates – that could only be derived from a graphical illustration provided by the applicant – it appears that the lower limits of the 95% CI would clearly not exceed the 20% threshold identified by the applicant.

Newly introduced risk-mitigation strategies will include a modified titration regimen. Reference is made to a detailed discussion of the so called "enhanced titration regimen" in the safety sections. No efficacy

data are available with the modified dosing regimen. As discussed elsewhere, the similar PK/PD profile significantly reduces this uncertainty.

6.4. Unfavourable effects

The grounds for refusal of donanemab with regard to safety are based on the occurrence of amyloid-related imaging abnormalities (ARIA) in the donanemab programme in a significant proportion of treated patients and the clinical consequences deriving thereof, which may be serious and potentially fatal. In general, the incidence and severity of ARIA-E and -H increases with the number of APOE4 alleles. The applicant provided a post-hoc analysis for ARIA as the key unfavourable effect separated by APOE4 carrier status (homozygotes, heterozygotes, and noncarriers of APOE4) as well as APOE4 noncarriers and heterozygotes combined, for which the applicant seeks approval.

ARIA-E and ARIA-H occurred with very common frequency for all APOE4 genotypes. ARIA-E and ARIA-H occurred isolated or concurrent with each other.

ARIA-E was observed in 20.6% (146/710) of the proposed indicated population treated with donanemab and in 1.8% (13/728) patients on placebo.

In the donanemab group, APOE4 homozygotes had a higher incidence of **ARIA-E** (41.3% vs. 3.4% for placebo). After removal of APOE4 homozygotes from the analyses, the incidence was halved in both treatment groups, donanemab and placebo. The incidence of ARIA-E in the long-term extension (LTE) of study AACI, which includes patients treated with donanemab during AACI-PC as well as patients, who were treated with placebo during AACI-PC and switched to donanemab during the LTE, was consistent with the placebo-controlled period.

Most cases of ARIA-E occurred within the first 24 weeks of treatment and did not increase with longer treatment of up to 36 months in the combined AACI-PC and AACI-LTE period, irrespective of APOE4 genotype; this is also supported by an analysis of long-term safety data in patients (from the overall population) continuously treated with donanemab beyond 18 months in the LTE.

A majority of events resolved during a median time of 2 months (mean time to resolution 72.4 days). Radiographic severity of ARIA-E events was mainly mild or moderate and rated severe in 1.4% of APOE4 noncarriers and heterozygotes during the 18 months treatment period in study AACI-PC and did not change during AACI-PC and AACI-LTE periods combined.

In the proposed indicated population, the incidence of **serious ARIA-E** and **symptomatic ARIA-E** was 1.3% (0% for placebo) and 5.6% (0% for placebo) in study AACI-PC, and both did not increase during the combined treatment periods in study AACI-PC and its LTE (over up to 36 months).

Based on the totality of ARIA-E events in the proposed indicated population (N=146) in study AACI-PC, 9 were serious (6%), and 40 were symptomatic (27%). All of the 9 reported ARIA-E SAEs were symptomatic, and two of them resulted in a fatal outcome. Both patients were APOE4 heterozygotes and were reported with severe ARIA-E, one of whom also had severe ARIA-H and potential baseline risk factors (e.g. hypertension). Death occurred after the patient was rechallenged following dosing interruption. The other fatal SAE occurred under an early protocol with less frequent MRI monitoring. During the LTE, there was one additional fatal ARIA-E event in an APOE4 heterozygote patient treated with placebo during AACI-PC. Delayed treatment with steroids was reported. The patient had a medical history of hypertension as a possible risk factor.

The most commonly reported symptoms with ARIA-E were headache, confusional state, dizziness, nausea, and also seizure. Seizures were reported in N=5 patients. More than 75% of symptomatic ARIA-E events were mild or moderate. Severe symptomatic ARIA-E in the proposed indicated

population (APOE4 noncarriers and heterozygotes) in AACI-PC occurred in 5 patients, and involved, seizures, delirium, bradycardia, acute respiratory failure, movement disorder, hemiplegia, headache, and altered state of consciousness.

Most subjects experienced a single ARIA-E event, while 4.9% (35/710) of the proposed indicated population treated with donanemab experienced recurrence of ARIA-E (i.e. between 2 and 4 episodes). More specifically, 24% of patients with ARIA-E experienced a recurrent event (35 of 146 patients). Up to four ARIA-E episodes were reported in 4 patients.

ARIA-H was observed in 27.6% (196/710) of patients from the proposed indicated population treated with donanemab. A majority of ARIA-H events was asymptomatic (96%), and only 4% of ARIA-H events were symptomatic. Symptoms of ARIA-H were not systematically collected, as they were difficult to distinguish from ARIA-E when ARIA-E and ARIA-H co-occurred (reference is made to the CHMP AR).

Isolated ARIA-H (in the absence of ARIA-E) was reported with similar incidence for donanemab and placebo in the proposed indicated population (12.4% and 11.5%), while ARIA-H concurrent with ARIA-E was more frequently observed with donanemab as compared to placebo (12.7% vs. 0.4%). Overall, based on radiographic results, almost half of the ARIA-H events (46%) were concurrent with ARIA-E.

Most of the (first) ARIA-H events were reported within 24 weeks of treatment, while subsequent ARIA-H episodes occurred early in treatment and throughout study AACI-PC, based on the data for the overall population. Moreover, isolated ARIA-H was observed throughout the treatment period. Therefore, changes of the MRI monitoring were requested. The SmPC now recommends **MRI monitoring** prior to the second (at 1 month), third (at 2 months), fourth (at 3 months) and seventh (at 6 months) dose. An additional MRI at one year of treatment (prior to the twelfth dose) should be performed in patients with ARIA risk factors such as ApoE ε4 heterozygotes, and/or patients with previous ARIA events earlier in treatment. Clinical evaluation including an MRI should be performed at any time during treatment when symptoms suggestive of ARIA occur.

The incidence of ARIA-H in the AACI-LTE was slightly higher as compared to the AACI-PC period (34.2%), mainly driven by a higher incidence of isolated ARIA-H with donanemab in the proposed indicated population (17.3% in the AACI-PC and AACI-LTE combined versus 12.4% in the AACI-PC period alone). Likewise, an analysis of long-term safety in patients (from the overall population) continuously treated with donanemab beyond 18 months in the LTE revealed an increase in ARIA-H events, while at the same time the observation time-adjusted incidence rate slightly decreased.

In 72% of patients with ARIA-H, the radiographic severity was mild or moderate, and rated as severe in 7.6% of patients in the proposed indicated population (severe ARIA-H microhaemorrhage is defined as ≥ 10 treatment-emergent total microhaemorrhages or new incident microhaemorrhages, whichever is greater and ARIA-H superficial siderosis > 2 new or increased focal areas of superficial siderosis). Radiographic severity remained roughly similar over the 36 months period in the AACI-PC and AACI-LTE studies combined (9.3% of ARIA-H events were rated as severe).

In the proposed indicated population, **serious ARIA-H** and **symptomatic ARIA-H** events occurred with an incidence of 0.3% (0% for placebo) and 1.1% (0.3% for placebo) in study AACI-PC. Based on the totality of ARIA-H events in the proposed indicated population (N=196), 2 were serious (1%), and 8 were symptomatic (4%). Both ARIA-H SAEs were fatal, including one patient (APOE4 heterozygote) with concurrent serious and severe ARIA-E (who was rechallenged with donanemab despite these findings; see above), and another patient (APOE4 noncarrier) who died after haemorrhagic stroke (baseline finding of superficial siderosis plus potential vascular risk factors, e.g. hypertension).

No increased incidences of serious ARIA-H or symptomatic ARIA-H were noted when AACI-PC and AACI-LTE results are combined up to 36 months of treatment.

The majority of patients experienced a single ARIA-H event, while 9.9% (70/710) of the proposed indicated population treated with donanemab experienced recurrence of ARIA-H (i.e. between 2 and 4 episodes). More specifically, 35.7% of patients with ARIA-H experienced a recurrent event (70 of 196 patients). Up to four ARIA-H episodes were reported in 2 patients.

In the proposed indicated population in study AACI-PC**, intracerebral haemorrhage (ICH) > 1cm in diameter** occurred with an incidence of 0.4% in the donanemab group (3/710 patients) and 0.3% in the placebo group (2/728 patients). One of the events in either group was reported as SAE, none of which was fatal. However, one fatal thalamic haemorrhage was reported in Study AACI -A9 in an APOE4 heterozygote patient with various cardiovascular risk factors. Four additional events of ICH > 1 cm occurred in the AACI-LTE (one event in a noncarrier and three events in APOE4 heterozygotes). Overall, the incidence of ICH > 1 cm in AACI-PC and AACI-LTE combined was 0.6%. One of two ICH > 1 cm events reported as SAE was fatal (in an APOE4 heterozygote; death was attributed to acute ischaemic stroke, while the patient died from multiple intracranial haemorrhages after receiving tenecteplase). Section 4.4 of the SmPC includes a warning with regard to initiation of thrombolytics in patients treated with donanemab and description of ICH as an ADR is added in section 4.8.

A **modified titration regimen** has been evaluated in **study AACQ**, which differed from the standard titration only in the first three doses of donanemab, i.e. instead of three doses of 700 mg, dosing starts with 350 mg, followed by 700 mg as the second dose and 1050 mg as the third dose. Overall exposure within the 3-months titration period remained therefore identical to the standard titration, supported by comparable cumulative exposure and similar observed brain amyloid plaque reduction at Week 24 and Week 52.

At Week 52 in the proposed indicated population, the incidence of **ARIA-E** was lower in the modified titration group as compared to the standard dosing group (14.7% vs. 20.4%), i.e. a relative risk reduction of 28%. No radiographically severe and severe symptomatic ARIA-E occurred in the modified titration arm (versus 3 patients in the standard arm). Moreover, a relative risk reduction of ~35% and ~56% was observed for symptomatic ARIA-E and recurrent ARIA-E in the modified arm as compared to standard dosing. The time-to-onset of ARIA-E for both titration regimens was in line with the data from study AACI-PC. A 30% relative risk reduction has also been observed with the modified titration scheme as compared to standard titration for **ARIA-H concurrent with ARIA-E** (incidence: 9.9% vs. 14%). Symptomatic ARIA-H occurred in a single patient in study AACQ (modified titration arm), and none of the ARIA-H events was rated as serious.

Two patients were reported with events of **ICH > 1 cm** in the modified titration group (1%) and one patient in the standard dosing group (0.5%). One of the two patients in the modified titration arm was a noncarrier and the event was asymptomatic. The other patient was an APOE4 heterozygote with a SAE of middle cerebral artery stroke (rated as related to donanemab) following mild ARIA-E and 6 new microhaemorrhages after the 6th dose of donanemab. Death occurred following an intraparenchymal haemorrhage after administration of a tissue plasminogen activator (i.v. tenecteplase).

In study AACI-PC, ~10% of patients on donanemab received concomitant anticoagulant treatment at baseline. The effect of antithrombotic medication (including aspirin, non-aspirin antiplatelets, and anticoagulants) on ARIA-H and macrohaemorrhage severity did not reveal a clear pattern different than that observed for antithrombotics overall, although numbers were small. However, there is a plausible risk for worsening of ARIA-H and macrohaemorrhages with anticoagulant treatment, in line with other ATT products which justifies a contraindication for initiation in patients receiving ongoing anticoagulant therapy.

Six of the **seven death cases** that were either related to ARIA (4 events) or ICH (3 events) in the proposed indicated population occurred in APOE4 heterozygotes and only one in an APOE4 noncarrier. Upon re-evaluation of these fatalities, a number of communalities/ risk factors have been identified:

the four fatalities concerning ARIA-E and ARIA-H presented as radiographically severe (3 of 4 cases), were symptomatic, and in three of them, a medical history of hypertension/ worsening of hypertension during treatment with donanemab was reported. These risks are now addressed by additional risk minimisation measures, i.e. including the recommendation to permanently discontinue donanemab in patients with severe asymptomatic and symptomatic ARIA (Table 1 in the SmPC), and to include poorly controlled hypertension as a contraindication for treatment with donanemab, in line with the findings of Zimmer et al. (2025) and as proposed by Rabinoivici et al. (2025). Of the three fatalities concerning brain haemorrhages, two occurred after treatment with thrombolytics for stroke. Initiation of thrombolytic treatment in patients treated with donanemab remains of concern. The warning with regard to concomitant administration of thrombolytics in section 4.4 addresses the need for a dose pause for donanemab and careful benefit/risk assessment. Moreover, two of the three fatalities due to brain haemorrhages had a medical history of hypertension, which is a risk factor for ICH.

6.5. Uncertainties and limitations about unfavourable effects

Restricting the overall population to noncarriers and heterozygotes of APOE4 results in a population that accounts for 83% of the overall population, which appears to be a representative number to characterise the risk of ARIA in this subgroup. This restriction to a subgroup, in the context of a trial with statistically compelling results in the overall population, biological credibility of the subgroup effect and similar results in the literature with other medicines in the class appears well justified. However, a small uncertainty remains in the precise estimation of the risk reduction deriving from the restriction.

The long-term consequences of ARIA in terms of cognitive outcomes and disease progression are also to be better characterised, and this is one of the objectives of the category 1 PASS *Registry-based observational study to characterise ARIA within a cohort of donanemab treated patients in the EU*.

6.6. Effects Table

Table 67. Effects table for Kisunla, indicated for the treatment of adult patients with a clinical diagnosis of mild cognitive impairment and mild dementia due to Alzheimer's disease (Early symptomatic Alzheimer's disease) who are apolipoprotein E ε4 (ApoE ε4) heterozygotes or non-carriers with confirmed amyloid pathology[#] (see section 4.4) based on MI with hybrid approach: Jump-to-Reference (J2R) for missing data due to death or severe, symptomatic, or serious ARIA events, and Copy Increments in Reference (CIR) for other reasons (efficacy database lock: 28 April 2023; safety data cut-off: 30 August 2024).

Effect	Short Description	Unit	Donanemab	Placebo	Uncertainties/ Strength of evidence	References
Favourable Effects						
iADRS	LS mean change (SE) at Week 76		-10.82 (0.577)	-13.47 (0.575)	SoE: Uncertainties with regard to the imputation method and its influence on effect sizes has been resolved by using different imputation methods, including the hybrid imputation method requested during the re-examination procedure.	Study AACI, applicant re-examination document
	LS Mean Change Difference at Week 76 (SE) [95% CI]		**2.65 (0.820) [1.035, 4.256]**			
CDR-SB	LS mean change (SE) at Week 76		1.73 (0.096)	2.42 (0.097)		Study AACI, applicant re-examination document
	LS Mean Change Difference at Week 76 (SE) [95% CI]		**-0.69 (0.133) [-0.950, -0.427)**			
Unfavourable Effects						

Effect	Short Description	Unit	Donanemab	Placebo	Uncertainties/ Strength of evidence	References
			Donanemab **N=710 (APOE4 noncarriers and heterozygotes)**	**Placebo** **N=728 (APOE4 noncarriers and heterozygotes)**		
Deaths due to any ARIA/ICH > 1 cm	Incidence in APOE4 noncarrier and heterozygotes	n	7	0	Unc.: 1 noncarrier and 6 APOE4 heterozygotes several risk factors identified (severe ARIA, medical history of hypertension; antithrombotic treatment, contraindications for treatment with donanemab).	All-Dona analysis set
ARIA-E - Symptomatic ARIA-E	Incidence in APOE4 noncarrier and heterozygotes	n %	146 (20.6) 40 (5.6)	13 (1.8) 0	SoE: reduction of ARIA-E events by ~50% in the proposed indicated population as compared to APOE4 homozygotes; TTO within the first 24 weeks. Unc: permanent discontinuation of treatment in patients with radiographically severe ARIA-E with or without symptoms	Study AACI-PC

Effect	Short Description	Unit	Donanemab	Placebo	Uncertainties/ Strength of evidence	References
	Incidence in APOE4 noncarrier and heterozygotes	n %	**Standard dosing (N=186)**: 38 (20.4) Symptomatic ARIA-E: 9 (4.8)	**Modified titration (N=191)**: 28 (14.7) Symptomatic ARIA-E: 6 (3.1)	SoE: relative risk reduction in ARIA-E events of ~28% with modified titration as compared to standard titration in the proposed indicated population. Relative risk reduction in symptomatic ARIA-E events of ~35% with modified titration as compared to standard titration in the proposed indicated population.	Study AACQ
ARIA-E SAE	Incidence in APOE4 noncarrier and heterozygotes	n %	9 (1.3)	0	All SAEs were symptomatic	Study AACI-PC

Effect	Short Description	Unit	Donanemab	Placebo	Uncertainties/ Strength of evidence	References
ARIA-H - Symptomatic ARIA-H - Isolated ARIA-H	Incidence in APOE4 noncarrier and heterozygotes	n %	196 (27.6) 8 (1.1) 88 (12.4)	89 (12.2) 2 (0.3) 84 (11.5)	SoE: reduction of ARIA-H events by ~50% in the proposed indicated population as compared to APOE4 homozygotes; TTO within the first 24 weeks, and further episodes also occur early during treatment. Isolated ARIA-H occurs throughout the treatment period requiring an additional MRI after 12 months.	Study AACI-PC
ARIA-H SAE	Incidence in APOE4 noncarrier and heterozygotes	n %	2 (0.3)	0	Both SAEs were fatal	Study AACI-PC

Effect	Short Description	Unit	Donanemab	Placebo	Uncertainties/ Strength of evidence	References
Intracerebral haemorrhage > 1 cm	Incidence in APOE4 noncarrier and heterozygotes	n %	3 (0.4)	2 (0.3)	SoE: rate of ICH>1 cm in PBO arms of AD studies ranges from 0.4% – 1% (Honig et al., 2024) Unc: ICH > 1 cm occurs throughout the treatment period questioning the need for an additional MRI after 12 months. Increased risk for ICH>1 cm with concomitant use of antithrombotic agents, esp. thrombolytics.	Study AACI-PC

Abbreviations: iADRS = integrated Alzheimer's Disease Rating Scale; CDR-SB = Clinical Dementia Rating Scale – Sum of Boxes; SE = standard error.
Notes: MMRM analysis in ITT population, APOE4 = apolipoprotein E4 variant, ARIA-E = amyloid-related imaging abnormality-oedema/effusion, ARIA-H = amyloid-related imaging abnormality- haemorrhage; ICH = Intracerebral haemorrhage; SAE = serious adverse event
Notes: APOE4 Noncarrier and Heterozygous Carrier subpopulation analyses are post-hoc analyses; ARIA-E is defined as events of oedema/ effusions; ARIA-H is defined as events of microhaemorrhage and haemosiderin deposits.
Restricted indication as per re-examination application.

6.7. Benefit-risk assessment and discussion

6.7.1. Importance of favourable and unfavourable effects

Importance of favourable effects and the associated uncertainties

Alzheimer's disease is a devastating, chronically progressive and ultimately fatal neurodegenerative disease with very limited treatment options to date. Therefore, there is an urgent need for effective therapeutic options that influence the course of Alzheimer's disease.

Donanemab belongs to the emerging class of amyloid-targeting therapies for which the mechanism of action is the clearance of amyloid plaques. By clearing the brain parenchyma from amyloid plaques, donanemab aims at modifying the underlying pathology and slow cognitive and functional decline in patients with early Alzheimer’s Disease.

For marketing authorisation (initial application and re-examination), the applicant presented results from a single pivotal trial (AACI-PC) and from its long-term extension (LTE). This study included 1,736 patients with early Alzheimer’s disease who tested positive for amyloid pathology and who received either donanemab or placebo. For the re-examination, the target population was changed to a subgroup of patients with only one (heterozygotes) or no copy (non-carriers) of the ApoE4 gene. The main measure of effectiveness was a change in symptoms after 76 weeks, measured using the integrated Alzheimer’s disease rating scale (iADRs). The key secondary efficacy endpoint was the more established Clinical Dementia Rating- Sum of Boxes (CDR-SB).

In order to address remaining uncertainties regarding the size of the treatment effect, analyses using a different imputation method have been presented during the re-examination: a more conservative “hybrid” approach, using J2R for missing data due to severe/ symptomatic ARIA or death, and CIR for other grounds of missing data. With this hybrid approach of imputation, the mean difference in change from baseline in iADRS at week 76 between donanemab and placebo in the selected target population was 2.65 (95%CI: 1.035,4.256), which corresponds to a 19.6% slowing of iADRS deterioration. The mean difference in change from baseline in the CDR-SB at week 76 between donanemab and placebo in the new target population was -0.69 (95%CI: -0.950,-0.427), which corresponds to a 28.5% slowing of CDR-SB deterioration. These analyses confirmed the favourable treatment effect and its robustness to deviations from the assumptions of the estimators first presented.

The clinical significance of the effect has been supported by analyses including a responder analyses, that showed that significantly more placebo patients worsened to the next stage of the disease withing the observation period compared to donanemab treated patients, corresponding to a 38% lower risk of progressing to a worse stage of CDR-G with donanemab treatment in the heterozygotes and noncarriers (HR:0.62; p<0.0001).

Kisunla treatment will be terminated when amyloid plaques are cleared (e.g. at 6 or 12 months) as confirmed using a validated method. The maximum treatment duration will be 18 months which should not be exceeded even if plaque clearance is not confirmed. The applicant presented simulations which showed positive long-term effects after cessation of treatment.

Based on similar PK/PD the modified regimen can be assumed to have a similar efficacy profile as the one tested in the pivotal study. While a slightly delayed treatment effect cannot be ruled out, this might be acceptable if the risk of ARIA-E and of ARIA-H+ARIA-E is substantially reduced.

There is therefore a general agreement on the demonstration of a clinical benefit for the target population of heterozygotes and noncarriers.

Importance of unfavourable effects and the associated uncertainties

The safety profile of donanemab is driven by the frequent occurrence of ARIA (-E and –H) events, which is a known class effect of anti-amyloid treatment (Yadollahikhales and Rojas, 2023). The proposed indication for donanemab accounts for the fact that the risk of ARIA-E and ARIA-H is highest in APOE4 homozygotes and therefore only includes APOE4 heterozygotes and noncarriers.

ARIA events were mostly asymptomatic and of radiographically mild or moderate severity; however, symptomatic and also serious ARIA occurred more frequently than with placebo and – by genotype – more frequently in APOE4 homozygotes as compared to APOE4 heterozygotes and noncarriers. Symptomatic ARIA mainly presented with headache, confusional state, dizziness, and nausea; however, delirium, alteration of consciousness and also seizures rarely occurred as severe presentation, for which information is included in the proposed SmPC. Also, intracerebral haemorrhage >1 cm, including haemorrhagic stroke and cerebral haemorrhage, was observed in patients treated with either donanemab (0.4%) or placebo (0.3%) in the proposed indicated population; thus, the incidence with donanemab remains within the placebo rates from AD trials as referenced by Honig et al. (2024), ranging from 0.4% – 1%. The observations from the OLE and post-marketing data up to 9 months (from the US market and Japan, where the unrestricted population is eligible for treatment with donanemab) indicate that ARIA-E and ARIA-H (concurrent with ARIA-E) most frequently occur within the first 24 weeks of treatment and contribute to the findings in the clinical studies with regard to the incidences and presentations of ARIA, but also to the occurrence of ARIA-related symptoms like seizures and rarely fatal events with donanemab treatment. Also, events of ICH have been reported in the post-marketing setting but background information is scarce.

There is reasonable evidence that the incidence and severity of ARIA events also depend on the severity of clinical AD symptoms, potentially because of the increasing burden of CAA with advancing AD (CAA is a significant risk factor for ARIA). This has been concluded based on the treatment of patients with another ATT drug in clinical practice (Paczynski et al., 2025).

Patients with Alzheimer's disease can have several risk factors that predestine them for ARIA events or ICH >1 cm, especially with ATT treatment, i.e. higher age, APOE4 genotype, a history of stroke or cerebral microhaemorrhages, antithrombotic/ anticoagulant use, and vascular risk factors (e.g. hypertension). Therefore, determination of eligibility for treatment with donanemab as well as the application of appropriate risk minimisation (including monitoring and management of ARIA) is crucial.

The most important risk factor for ARIA especially in patients treated with anti-amyloid treatment is the APOE4 homozygote genotype that predisposes patients for ARIA being more likely symptomatic and severe as compared to patients being APOE4 heterozygote and noncarriers (Doran et al., 2024).

Thus, restricting the indication to APOE4 noncarriers and heterozygotes is reasonable to reduce the risk of severe, serious, symptomatic, and also recurrent ARIA-E and ARIA-H events. However, the incidence of ARIA with donanemab still remains higher in the proposed indicated population as compared to placebo. Of note, for ARIA-H, several studies imply a prevalence between 9.2% and 33% in patients with AD *not* treated with ATTs (Raman et al., 2014; Yaari et al., 2022). Notwithstanding, further risk factors to avoid serious and even fatal consequences of ARIA and ICH need to be taken into account in the proposed indicated population. Specifically, 6 of the 7 deaths reported and related to ARIA or ICH occurred in APOE4 heterozygotes and one fatality in a noncarrier. Risk minimisation measures that have the potential to prevent fatal outcomes according to the literature including additional newly introduced measures include:

- Frequent mandatory MRIs during the first 24 weeks of treatment (prior to the 2nd, 3rd, 4th and 7th dose). Additionally, a follow-up MRI after 12 months of treatment in patients with ARIA risk

factors, such as the APOE4 heterozygotes, and patients with previous ARIA events earlier in treatment. The latter can trigger recurrent ARIA events.

- Permanent discontinuation of donanemab in patients presenting with radiographically severe ARIA, with or without symptoms (since severe ARIA was noted in at least 3 cases with fatal outcome.
- Treatment with donanemab should not be initiated in patients with poorly controlled hypertension, which has been discussed as a potential risk factor for ARIA (Zimmer et al. 2025; Sperling et al. 2011).
- Treatment with donanemab should not be initiated in patients with ongoing anticoagulant therapy: antithrombotic use is a significant risk factor for developing ARIA-H and ICH (Doran et al., 2024). Thus, a contraindication in the product information in line with other ATT products and recommendations by Rabinovici et al. (2025) was implemented.

The set of risk minimisation measures has been improved during the re-examination procedure, and it is now considered satisfactory.

Moreover, despite not being evaluated in the pivotal study AACI-PC, a modified titration regimen for the first three doses of donanemab providing the same exposure and amyloid reduction as compared to the standard titration (thus allowing bridging of efficacy) offers an additional tool for risk minimisation, mainly regarding the reduction of ARIA-E events. The proposed potential mechanisms imply (1) a slower removal of vascular amyloid due to reduced antibody binding at lower initial doses leading to a reduction in leakiness and inflammation, and (2) a slower increase in donanemab serum concentration resulting in more gradual mobilisation of amyloid via the perivascular spaces, which limits exacerbation of CAA (Wang et al.,2025). Notwithstanding, the patient population in study AACQ slightly differed from the one in the pivotal study AACI-PC in that (1) the disease severity status in patients treated in the AACQ study was milder, (2) patients in study AACQ appear less cognitively impaired than those in study AACI-PC based on the mean MMSE score (25.14 in AACQ vs. 22.43 in AACI-PC), (3) the mean baseline amyloid CL was lower in patients treated in AACQ as compared to AACI-PC (84.40 vs. 103.49). Therefore, it is hypothesised that the modified titration regimen might be even more effective in the reduction of ARIA (especially ARIA-E) in a patient population with higher amyloid baseline burden like the one included in study AACI-PC. This notion is additionally supported by the fact that APOE4 homozygotes, who generally exhibit a greater Aβ deposition, had the largest effect regarding the reduction of ARIA-E and also ARIA-H when applying the modified titration scheme in study AACQ. Therefore, and despite some limitations, these data justify the modified titration regimen as an additional risk minimisation measure and hence replace the standard titration scheme in section 4.2 of the SmPC.

With regard to brain volume loss, patients in study AACI with ARIA-E or ARIA-H showed a similar decrease in whole brain volume as those without ARIA-E or ARIA-H as the overall population.

In summary, exclusion of APOE4 homozygote carriers from treatment with donanemab, together with application of risk minimisation measures as well as additional risk minimisation measures are considered appropriate to reduce the risk of severe and symptomatic ARIA and its consequences for patients treated in clinical practice. The risk of isolated ARIA-H is addressed with measures such as the exclusion of patients receiving anticoagulation therapy, and the exclusion of patients with poorly controlled hypertension. Moreover, the additional measures, including frequent MRI monitoring, a controlled access programme, a Healthcare Professional Guide and Checklist, patient card, follow-up questionnaire, educational material, as well as the PASS studies to evaluate drug utilisation and prove the effectiveness of these measures (Category 1), and lastly, to assess effectiveness of additional risk

minimisation activities are considered extensive and appropriate to address the risk of ARIA and ICH with donanemab treatment post-marketing.

6.7.2. Balance of benefits and risks

Clinical benefit has been demonstrated. The treatment effect can be considered modest but robust.

ARIA-E and ARIA-H, which have been discussed in detail by the CHMP, are well known risks of the treatment. However, these risks can be substantially reduced, monitored and managed, specifically as a controlled access programme will be in place and treatment be limited to eligible patients with strict adherence to the contraindications listed.

6.7.3. Additional considerations on the benefit-risk balance

Throughout the procedure, the CHMP received several interventions from third parties. Overall, these third parties expressed their views about the epidemiology of Alzheimer disease, the unmet medical need, the scales for assessing efficacy of treatments, outcomes in the clinical trials with donanemab, the clinical relevance of the reported outcomes, the manageability of ARIA, the inequality in access to AD modifying treatments, and the desire to further the field of treatment options for AD.

The CHMP considered the interventions in the context of its assessment. The CHMP expresses full agreement with the stated unmet medical need in AD. Further, the observations put forward are known by the CHMP, and as such, do not have impact on the CHMP conclusions.

6.8. Conclusions

The overall benefit/risk balance of Kisunla is positive subject to the conditions stated in section 'Recommendations'.

Divergent position is appended to this report.

7. Recommendations following re-examination

Based on the arguments of the applicant and all the supporting data on quality, safety and efficacy, the CHMP re-examined its initial opinion and in its final opinion concluded by majority decision that the benefit-risk of Kisunla is favourable in the following indication:

Donanemab is indicated for the treatment of adult patients with a clinical diagnosis of mild cognitive impairment and mild dementia due to Alzheimer's disease (Early symptomatic Alzheimer's disease) who are apolipoprotein E ε4 (ApoE ε4) heterozygotes or non-carriers with confirmed amyloid pathology (see section 4.4).

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Other conditions and requirements of the marketing authorisation

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder (MAH) shall submit the first PSUR for this product within 6 months following authorisation.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- **Additional risk minimisation measures**

Prior to the launch of Kisunla in each Member State, the Marketing Authorisation Holder (MAH) must agree about the content and format of the educational programme, including communication media, distribution modalities, and any other aspects, with the National Competent Authority. The MAH shall also agree the details of the controlled access programme (CAP).

The controlled access programme is aimed at promoting the safe and effective use of donanemab by confirming the correct selection of patients based on relevant indication or diagnosis, the genetic profile, and available MRI. All patients will be registered in the CAP registration system prior to the initiation of donanemab treatment.

The educational materials are aimed at educating healthcare professionals and patients/caregivers of the potential and risk factors for the development of ARIA (-E/-H) including signs, symptoms, and management.

The MAH shall ensure that in each Member State where Kisunla is marketed, prior to launch and after launch, all healthcare professionals and patients/caregivers who are expected to prescribe/receive Kisunla have access to/are provided with the following educational materials:

- HCP educational materials
- Patient Card

Healthcare professionals' (HCP) educational materials:

The educational material for prescribers and radiologists shall contain a guide for HCPs and a prescriber checklist, including the following key elements:

HCP guide:

- Information about the conditions of the donanemab CAP. Donanemab treatment should be administered under the supervision of a multidisciplinary team trained in monitoring and management of ARIA and experienced in detecting and managing infusion related reactions to ensure adequate management of patients treated with donanemab.

- Donanemab use may cause ARIA (-E or -H), and patients should be instructed to seek medical advice immediately if signs or symptoms suggesting ARIA appear.

- Symptoms of ARIA may include, but are not limited to, headache, vomiting, unsteadiness, dizziness, tremor, confusion, visual disturbances, speech disturbances, worsening cognitive function, alteration of consciousness, and seizures, and may mimic stroke or stroke-like symptoms.

- ARIA -E and -H can both be classified as mild, moderate, or severe based on MRI, and as symptomatic or asymptomatic based upon the clinical symptoms. Most serious ARIA reactions occurred within 12 weeks of initiation of treatment. Standard supportive treatment, including corticosteroids may be considered in case of ARIA-E.

- Risk factors for ARIA -E or -H include pre-treatment cerebral microhaemorrhage, superficial siderosis and ApoE ε4 carrier status (homozygotes greater than heterozygotes) compared to non carriers. Donanemab is indicated in ApoE ε4 heterozygotes or non-carrier patients.

- Testing for ApoE ε4 carrier status is mandatory prior to initiating donanemab treatment to inform the risk of developing ARIA.

- Donanemab treatment should be initiated or continued as per the indication and contraindications described in sections 4.1 and 4.3 of the SmPC, respectively.

- Dosing recommendations and treatment discontinuation for patients with ARIA-E and ARIA-H should be followed as described in section 4.2 of the SmPC.

- Events of ARIA-H and intracerebral haemorrhage greater than 1 cm have been reported in patients on donanemab treatment. Caution should be exercised when considering the administration of antithrombotics or a thrombolytic agent to a patient on donanemab as this may increase the risk of bleeding in the brain as described in section 4.4 of the SmPC.

- Treatment with donanemab should not be initiated in patients receiving ongoing anticoagulant therapy.

- ARIA should be considered in the differential diagnosis of patients presenting with stroke-like symptoms.

- ARIA can cause focal neurologic deficits similar to those observed in an ischemic stroke. Clinicians treating ischemic stroke should consider whether such symptoms could be due to ARIA before giving thrombolytic therapy in a patient being treated with donanemab. MRI or identification of vascular occlusion can help identify that ischemic stroke rather than ARIA is the aetiology, and inform use of thrombolytics or thrombectomy when appropriate.

- The purpose and use of the patient card including the importance of carrying the card at all times and to provide to HCPs in emergency situations.

Prescriber checklist:

Prior to treatment initiation:

- Initiation of donanemab treatment in all patients should be captured in the "EU CAP Registration System" implemented as part of a controlled access programme.

- ApoE ε4 carrier status testing is mandatory to inform the risk of developing ARIA. The use of donanemab in ApoE ε4 homozygous carrier patients is not indicated (see section 4.1 of the SmPC).

- Patients treated with donanemab must be given the patient card and be informed about the risks of this medicinal product.

- The presence of amyloid beta pathology and a clinical diagnosis of either mild cognitive impairment due to AD or mild AD dementia should be confirmed prior to initiating donanemab treatment.

- MRI should be performed at baseline (within 6 months prior to initiating treatment) for risk factors of ARIA including presence of cerebral microhaemorrhage and superficial siderosis. The use of donanemab in patients with > 4 microhaemorrhages or superficial siderosis is contraindicated.

- Donanemab treatment should not be initiated as per the contraindications described in section 4.3 of the SmPC.

Monitoring during treatment:

- Treatment should be maintained until amyloid plaques are cleared (e.g. at 6 or 12 months, see section 5.1 of the SmPC) as confirmed using a validated method. The maximum treatment duration is 18 months which should not be exceeded even if plaque clearance is not confirmed.

- MRIs should be performed prior to the second dose, prior to the third dose, prior to the fourth dose, and prior to the seventh dose. An additional MRI at one year of treatment (prior to the twelfth dose) in patients with ARIA risk factors such as ApoE ε4 heterozygotes, and patients with previous ARIA events earlier in treatment, should be performed.

- In case of ARIA, please follow the recommendations for dosing interruptions described in section 4.2 of the SmPC. Additional MRI is indicated if ARIA symptoms occur. A follow-up MRI to assess for resolution (ARIA E) or stabilisation (ARIA H) should be performed 2 to 4 months after initial identification.

- Standard supportive treatment, including corticosteroids may be considered in case of ARIA E.

- Resumption of dosing or permanent discontinuation after ARIA-E resolution and ARIA-H stabilisation should be guided by clinical judgment including re-evaluation of risk factors.

- Donanemab should be permanently discontinued after serious ARIA-E, serious ARIA-H, intracerebral haemorrhage greater than 1 cm, or recurrent symptomatic or radiographically moderate or severe ARIA events.

Patient Card:

Key elements directed towards the patient/caregiver:

- The patient card should be kept with the patient/caregiver at all times, and it should be shared with other healthcare providers involved in their treatment including emergency situations.

- Treatment with donanemab may cause amyloid related imaging abnormalities (ARIA).

- Symptoms of ARIA may include, headache, confusion, dizziness, vision changes, nausea, aphasia, weakness, or seizure.

- Patients should seek medical attention or advice if symptoms of ARIA occur.

- Emergency contact details of family member or caregiver.
- Contact details of the prescriber.

Key elements directed toward HCPs involved in the patient's treatment:

- ARIA (detected by MRI) can cause focal neurologic deficits similar to those observed in an ischaemic stroke. Because ARIA occurs more commonly in the first 6 months of treatment with donanemab, clinicians treating ischemic stroke should consider whether such symptoms could be due to ARIA before giving thrombolytic therapy in a patient being treated with donanemab (For additional details see Kisunla SmPC section 4.4 ARIA and Concomitant antithrombotic treatment).

Controlled Access Programme

The MAH shall agree to the details of a Controlled Access Programme with each National Competent Authority and must implement such programme nationally to ensure that a Controlled Access Programme (CAP) promotes the safe and effective use of donanemab.

The Controlled Access Programme includes the following key principles that will be incorporated within each system in all Member States. These are:

(1) restricting access of donanemab to preselected centres and

(2) implementing a registration system to assist HCPs in

i. assessing patient eligibility,

ii. providing quick reference to educational materials, and

iii. confirming adherence to the materials.

The CAP allows for pre-selection of centres with required criteria, prescribers able to assess eligibility for donanemab, access to a validated method to assess brain amyloid pathology, access to IV infusions, access to MRI [scheduled and non-scheduled] to monitor for ARIA, and access ApoE ε4 tests). This will be followed by drug distribution to pharmacies of these selected centres with affiliated prescribers, who have received HCP educational materials on donanemab treatment. Prescribers within these centres will, prior to a patient receiving donanemab, use the registration system to

- attest to receiving and understanding the required HCP education guide,
- confirm that the (anonymised) patient meets required eligibility criteria per label,
- and verify that the patient has been counselled regarding the risks of donanemab and provided the patient card.

- **Obligation to conduct post-authorisation measures**

The MAH shall complete, within the stated timeframe, the below measures:

Description	Due date
Safety registry to characterise ARIA in donanemab-treated patients The MAH shall perform an observational registry study to provide safety data on donanemab in routine practice, with a focus on characterising the incidence and severity of symptomatic ARIA (primary objective) and asymptomatic ARIA (secondary objective). Patients with ARIA events will be followed to assess interventions and resolution (ARIA-E) or stabilisation (ARIA-H) timelines as well as longer term cognitive outcomes and impact on disease progression. In	Final report: 31 December 2031

addition, the incidence of hypersensitivity events and intracranial haemorrhage will be described. Intracranial haemorrhage will also be evaluated in the subgroup of patients receiving concomitant antithrombotic or thrombolytic therapy.	
Secondary database study to characterise donanemab-treated patients The MAH shall perform an observational cohort study using secondary databases aimed at providing data on donanemab in routine practice. The focus of this study is on characterising the incidence of hypersensitivity events and intracranial haemorrhage events, describing utilisation of donanemab, and assessing measures such as MRI receipt, patient population treated and dosing paradigms to support assessment of effectiveness of risk minimisation measures.	Final report: 31 December 2030

Conditions or restrictions with regard to the safe and effective use of medicinal product to be implemented by the member states

The Member States should ensure that all conditions or restrictions with regard to the safe and effective use of the medicinal product described below are implemented.

- **Additional risk minimisation measures**

  1. Educational package

  The Member States shall ensure that prior to Kisunla being marketed, all healthcare professionals who are expected to prescribe the medicinal product and patients who will use it, have access to/are provided with the educational package which should include the key elements agreed.

  2. Controlled Access Programme

  The Member States shall ensure that a controlled access programme (CAP) to promote the safe and effective use of Kisunla. The CAP includes the following key principles that will be incorporated within each system in all Member States. These are restricting access of donanemab to preselected centres and implementing a registration system to assist HCPs in assessing patient eligibility, providing quick reference to educational materials, and confirming adherence to the materials.

  The MAH shall agree the details of the controlled access programme with each National Competent Authority and must implement such programmes nationally.

New Active Substance Status

Based on the CHMP review of the available data, the CHMP considers that donanemab is to be qualified as a new active substance in itself as it is not a constituent of a medicinal product previously authorised within the European Union.

Divergent position(s)

Divergent position to the majority recommendation is appended to this report.

8. Appendices

8.1. Divergent position(s) to the majority recommendation

The undersigned members of CHMP did not agree with the CHMP's opinion recommending the granting of a Marketing Authorisation for donanemab in the treatment of adult patients with a clinical diagnosis of mild cognitive impairment and mild dementia due to Alzheimer's disease (Early symptomatic Alzheimer's disease) who are apolipoprotein E ε4 (APOE ε4) heterozygotes or noncarriers with confirmed amyloid pathology.

The unmet need for a treatment of Alzheimer's disease (AD) is fully acknowledged, however, undersigned members consider that the B/R of donanemab is negative for the following reasons:

- The evidence in this MAA comes from a single pivotal study with a pharmacological rationale that is insufficiently justified. With a single pivotal trial, results are expected to be particularly compelling with respect to clinical relevance, and not only statistical significance. There is a strong need to have a clear demonstration that targeting existing cerebral amyloid can delay the progressive disease course of AD in terms of both cognition and function, which is not convincingly demonstrated in this case.
- Despite statistical significance in the primary efficacy evaluation, the magnitude of the resulting effect size, expressed as group difference in mean change to baseline iADRS score is small and hence questionable in relation to clinical relevance. In the context of published minimal clinically important difference of 5 points (for MCI) and 9 points (for mild AD) on this scale for individual patient changes, the resulting difference in mean changes on the group level of 2.65 points (95% CI: 1.04, 4.26) appears too low.
- The focus on post-hoc selected favourable efficacy results for some of the predefined secondary endpoints (in particular, CDR-based endpoints) bears the potential of overestimation and overinterpretation of the beneficial effects of donanemab.
- When expressing the treatment effects as %-slowing of progression, the conclusion that a minimally relevant threshold of 20% slowing was reached is not supported. Due to the uncertainty of effect estimation based on the lower limit of the confidence interval a slowing of effect of less than 10% cannot be excluded following the primary endpoint analysis.
- Considerable uncertainty remains in relation to the projection of long-term efficacy outcome. Uncertainty remains with precision and reliability of long-term estimates due to the lack of a direct within-study head-to-head comparison. Comparison to external control data was not possible for iADRS, the primary efficacy endpoint of the pivotal trial.
- Although the ApoE ε4 homozygous patients were excluded from the target population, the incidence of ARIA in the restricted population is substantial, with ARIA events occurring very commonly, even with the modified dosing (all ARIA: 28.8% [ARIA-E: 14.7%, ARIA-H: 24.6%]). Although most patients experience an asymptomatic, and radiographically mild to moderate ARIA event, an important number of patients experience serious ARIA-E (0.5%) and/or symptomatic ARIA-E (3.1%) or symptomatic ARIA-H (0.5%), which can include seizure and intracranial haemorrhage. These most harmful events cannot be expected to be prevented by restricting the target population and modifying the dosing.
- The majority (6/7) of fatal events related to ARIA/ICH>1cm across the clinical programme of donanemab occurred in heterozygotes, and one in a non-carrier. These data do not support the conclusion of heterozygotes and non-carriers being a credible subgroup for minimizing the risk for potentially serious and life-threatening ARIA events. Post-marketing data from US and Japan suggest that even overall ARIA events were more frequently observed in heterozygotes

(47%-50%) compared to non-carriers (21-24%) or homozygotes (29%).

- Several risk minimisation measures (RMM) are proposed to be implemented, which may help to select the correct patients (ApoE ε4 status of the patient and lack of contra-indications of the product) and inform patients about the risks. These, however, would not change the risks seen with donanemab; even if RMMs are applied correctly, a substantial group of patients in the target population would still experience ARIA, including fatal events.
- The proposed PASS may provide post-approval information on (long-term) patient safety, but neither a registry-based observational study, secondary database study, or healthcare provider survey are deemed suitable to inform the relationship between ARIA, risk mitigation, and the occurrence of serious ARIA or fatalities. Furthermore, the studies will not help minimise the risks, but will expose an only mildly progressed patient population to a potentially life-threatening treatment.

To conclude, the limited treatment effect achieved with donanemab does not outweigh the safety risk of potentially fatal events of ARIA in a population of ApoE ε4 heterozygotes or non-carriers with MCI or mild dementia due to AD.

Therefore, it is the opinion of the divergent CHMP members that the benefit-risk balance of Kisunla is negative.

Amsterdam, 24 July 2025

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