Report on the Deliberation Results

August 13, 2024
Pharmaceutical Evaluation Division, Pharmaceutical Safety Bureau
Ministry of Health, Labour and Welfare

Brand Name	Kisunla Intravenous Infusion 350 mg
Non-proprietary Name	Donanemab (Genetical Recombination) (JAN*)
Applicant	Eli Lilly Japan K.K.
Date of Application	August 18, 2023

Results of Deliberation

In its meeting held on August 1, 2024, the First Committee on New Drugs concluded that the product may be approved and that this result should be presented to the Pharmaceutical Affairs Council.

The product is classified as a biological product. The re-examination period is 8 years. The drug product and its drug substance are both classified as powerful drugs.

Approval Conditions

1. The applicant is required to develop and appropriately implement a risk management plan.
2. The applicant is required to conduct a post-marketing use-results survey covering all patients treated with the product to obtain information on patient characteristics until data from a specified number of patients have been accrued. Furthermore, the applicant should gather data on the safety and efficacy of the product early and take appropriate measures to ensure the proper use of the product.

**Japanese Accepted Name (modified INN)*

Review Report

July 19, 2024
Pharmaceuticals and Medical Devices Agency

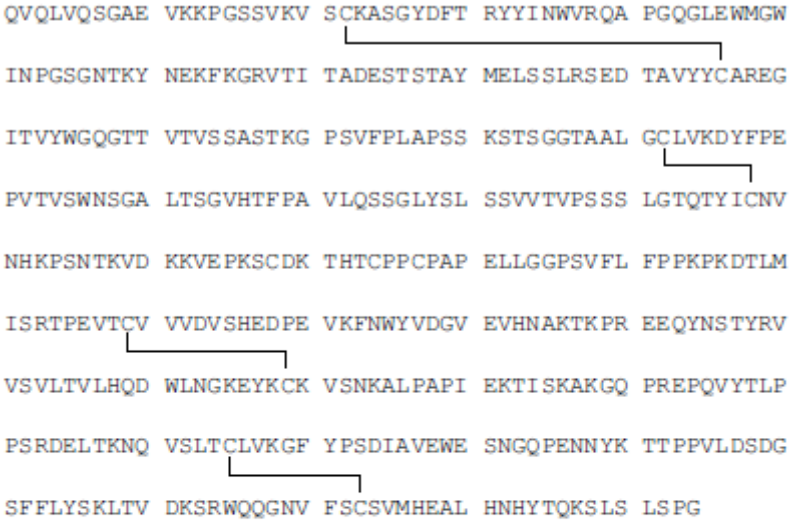
The following are the results of the review of the following pharmaceutical product submitted for marketing approval conducted by the Pharmaceuticals and Medical Devices Agency (PMDA).

Brand Name	Kisunla Intravenous Infusion 350 mg
Non-proprietary Name	Donanemab (Genetical Recombination)
Applicant	Eli Lilly Japan K.K.
Date of Application	August 18, 2023
Dosage Form/Strength	Injection: each vial contains 350 mg of donanemab (genetical recombination)
Application Classification	Prescription drug, (1) Drug with a new active ingredient
Definition	Donanemab is a recombinant anti-N-terminal pyroglutamyl amyloid beta peptides (3-x) monoclonal antibody whose complementarity-determining regions are derived from mouse antibody and other regions are derived from human IgG1. In the H-chain, K445 at the C-terminus is deleted. Donanemab is produced in CHO cells. Donanemab is a glycoprotein (molecular weight: ca. 148,000) composed of 2 H-chains (γ1-chains) consisting of 444 amino acid residues each and 2 L-chains (κ-chains) consisting of 219 amino acid residues each.

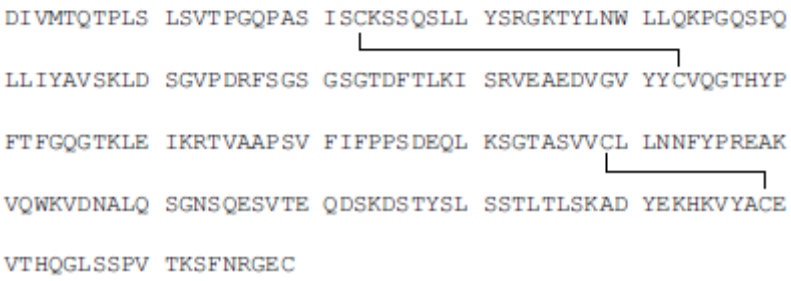
Structure

Amino acid sequence:

H H chain



L L chain



Intra-chain disulfide bonds: shown in solid lines

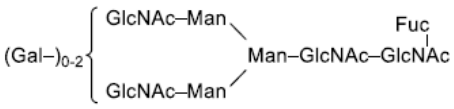
Inter-chain disulfide bonds: between H-chain C218 and L-chain C219, H-chain C224 and H-chain C224, H-chain C227 and H-chain C227

Partial processing: H-chain G444

Pyroglutamic acid (partial): H-chain Q1

Glycosylation: H-chain N295

Deduced structure of the major glycan:



Molecular formula: $C_{6452}H_{10012}N_{1708}O_{2016}S_{42}$ (protein moiety, 4 chains)

Molecular weight: approximately 148,000

Items Warranting Special Mention None

Reviewing Office Office of New Drug II

Results of Review

On the basis of the data submitted, PMDA has concluded that the product has efficacy in slowing progression of mild cognitive impairment and mild dementia due to Alzheimer's disease, and that the product has acceptable safety in view of its benefits (see Attachment).

As a result of its review, PMDA has concluded that the product may be approved for the indication and dosage and administration shown below, with the following conditions. Issues that should be further investigated include the incidence of amyloid-related imaging abnormalities (oedema/effusion, cerebral microhemorrhage, and superficial siderosis of the central nervous system) and cerebral haemorrhage; and safety profile in patients who are taking antiplatelets, anticoagulants, or thrombolytic medications.

Indication

To slow the progression of mild cognitive impairment and mild dementia due to Alzheimer's disease

Dosage and Administration

The usual adult dosage of donanemab (genetical recombination) is 700 mg administered as an intravenous infusion over at least 30 minutes every 4 weeks for the first 3 doses, and then 1400 mg every 4 weeks.

Approval Conditions

1. The applicant is required to develop and appropriately implement a risk management plan.
2. The applicant is required to conduct a post-marketing use-results survey covering all patients treated with the product to obtain information on patient characteristics until data from a specified number of patients have been accrued. Furthermore, the applicant should gather data on the safety and efficacy of the product early and take appropriate measures to ensure the proper use of the product.

Attachment

Review Report (1)

April 5, 2024

The following is an outline of the data submitted by the applicant and content of the review conducted by the Pharmaceuticals and Medical Devices Agency (PMDA).

Product Submitted for Approval

Brand Name	Kisunla Intravenous Infusion 350 mg
Non-proprietary Name	Donanemab (Genetical Recombination) (JAN*)
Applicant	Eli Lilly Japan K.K.
Date of Application	August 18, 2023
Dosage Form/Strength	Injection: Each vial contains 350 mg of donanemab (genetical recombination).

Proposed Indication

To slow the progression of mild cognitive impairment and mild dementia due to Alzheimer's disease

Proposed Dosage and Administration

The usual adult dosage of donanemab (genetical recombination) is 700 mg administered as an intravenous infusion every 4 weeks for the first 3 doses, and then 1400 mg every 4 weeks as an intravenous infusion until brain amyloid β plaques are cleared.

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List of Abbreviations

See Appendix.

1. Origin or History of Discovery, Use in Foreign Countries, and Other Information

Alzheimer's disease (AD) is clinically characterized by a gradual progression of overall cognitive decline. It has been shown, among other findings, that accumulation of amyloid plaques composed of amyloid β (Aβ) outside of neuron cells starts 10 to 20 years before the onset of the clinical symptoms of AD. Although the mechanism by which amyloid plaques cause AD symptoms has not been elucidated, it has been suggested that an imbalance between the production and removal of Aβ leads to the cerebral accumulation and deposition of Aβ, resulting in neurodegeneration, which is involved in cognitive decline. Mild cognitive impairment (MCI) due to Alzheimer's disease (MCI due to AD) is defined as the pre-dementia stage in which patients have AD pathology and MCI but do not have substantial difficulty with activities of daily living. However, patients with MCI due to AD may progress to a stage in several years in which cognitive impairment significantly affects activities of daily living. For this reason, it is important to slow the progression of AD in its early stages, including MCI due to AD.

Donanemab, which was developed by Eli Lilly and Company in the US, is a recombinant humanized immunoglobulin G1 (IgG1) monoclonal antibody targeting pyroglutamate modified amyloid β at the third amino acid of amyloid β (N3pG Aβ) that is considered to be present only in insoluble amyloid plaques. Donanemab slows the patient's clinical decline due to the progression of AD in patients with MCI due to AD and those with mild Alzheimer's disease dementia (AD-D) by selectively binding to N3pG Aβ and clearing amyloid plaques by microglial phagocytosis.

Eli Lilly and Company started the clinical development program for donanemab in 2013. As of March 2024, donanemab is under review in [redacted] countries and regions, including the EU and the US.

In Japan, the applicant began the clinical development of donanemab in 20[redacted]. Recently, the applicant has filed an application for marketing approval of donanemab with the proposed indication of "to slow the progression of mild cognitive impairment and mild dementia due to Alzheimer's disease" based on data including results from Study AACI, a global phase III study in patients with MCI due to AD or mild AD-D [see Section "7. Clinical Efficacy and Safety and Outline of the Review Conducted by PMDA"].

In the following sections, unless otherwise specified, "MCI due to AD and mild AD-D" are abbreviated as "early AD" [see Appendix].

2. Quality and Outline of the Review Conducted by PMDA

2.1 Drug substance

2.1.1 Generation and control of cell substrate

[redacted] libraries were constructed from human Aβ[redacted] peptide [redacted] cells derived from [redacted] [redacted] immunized with [redacted] of Aβ[redacted]. Based on the libraries and [redacted], an antibody was produced by optimization including improvement of affinity for Aβ[redacted]. Plasmids encoding heavy (H) chains and light (L) chains that were optimized based on the gene arrangement information for the antibody were constructed, and the expression constructs for donanemab

were generated from these plasmids. These expression constructs were transfected into Chinese hamster ovary (CHO) cells. A clone most suitable for the manufacture of donanemab was selected and used to prepare the master cell bank (MCB) and working cell bank (WCB).

The MCB, WCB, and cells at the limit of *in vitro* cell age (CAL) were subjected to characterization and purity tests in accordance with the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Q5A (R1), Q5B, and Q5D guidelines. The results demonstrated genetic stability during production. Within the range studied, no viral or non-viral adventitious agents were detected other than general endogenous retrovirus-like particles from rodent-derived cell lines.

Both the MCB and WCB are stored in vapor phase liquid nitrogen or at ≤ °C. While generation of a new MCB is not planned, a new WCB is generated as needed.

2.1.2 Manufacturing process

The manufacturing process of the drug substance consists of the following steps: culture flask expansion, seed culture, production culture, initial recovery, chromatography, viral inactivation/clarification, chromatography, chromatography, filtration, filtration, and dispensing/freezing/storage/testing.

, , , and have been defined as critical steps.

Process validation for the manufacturing process of the drug substance is performed on a commercial scale.

2.1.3 Safety evaluation of adventitious agents

With the exception of CHO cell lines, the host cells, no raw materials of biological origin are used in the manufacturing process of the drug substance.

Purity was tested on the MCB, WCB, and CAL [see Section “2.1.1 Generation and control of cell substrate”]. Bioburden testing, mycoplasma testing, *in vitro* virus testing, and mouse minute virus testing were performed on pre-harvest/unprocessed bulk manufactured on a commercial scale. Within the range studied, the tests detected no contamination caused by viral or nonviral adventitious agents. These tests on pre-harvest/unprocessed bulk are selected as the in-process control tests.

A viral clearance study was performed with model viruses for the purification process. The results demonstrated that the purification process has a sufficient viral clearance capacity (Table 1).

Table 1. Results of viral clearance study

Manufacturing process	Virus reduction factor (log_{10})			
	Porcine parvovirus	Xenotropic murine leukemia virus	Reovirus type 3	Pseudorabies virus
Viral inactivation/clarification by [redacted] treatment	[redacted]	[redacted]	[redacted]	[redacted]
[redacted] chromatography	[redacted]	[redacted]	[redacted]	[redacted]
[redacted] filtration[a]	[redacted]	[redacted]	[redacted]	[redacted]
Overall virus reduction factor	9.9	≥17.7	11.0	≥12.4

a, For [redacted] filtration step, data on [redacted] were used for data on [redacted], [redacted], and [redacted] as a worst case.

2.1.4 Manufacturing process development

For changes made to the manufacturing process during the development of the drug substance, comparability between pre-change and post-change drug substances have been evaluated in accordance with the ICH Q5E guidelines. The proposed drug substance was used for manufacturing of the formulation used in the phase III study.

2.1.5 Characterization

2.1.5.1 Structure and characterization

Table 2 summarizes the characterization performed.

Table 2. Evaluation items for characterization

Primary/higher order structure	Amino acid sequence, N-terminal and C-terminal amino acid sequence, post-translational modifications (glycosylation, deamidation, isomerization, oxidation, hydroxylation, glycation, N-terminal and C-terminal heterogeneity), disulfide bonds, free sulfhydryl content, secondary structure, tertiary structure, quaternary structure, thermal stability
Physicochemical properties	Molecular weight, charge variants, absorption coefficient, size variants, isoelectric point, IgG subclass analysis
Glycan structure	Glycosylation rate, glycan profiling, N-linked glycan structural analysis
Biological properties	Aβ[redacted] binding activity
	Fcγ receptor (I, IIa, and IIIa) binding activity, C1q binding activity, FcRn binding activity
	ADCP activity

The main evaluation results for biological properties were as follows:

- Using the [redacted] cell line, which stably expresses [redacted] receptors ([redacted]) and induces [redacted] response element-mediated [redacted] gene expression in the presence of Aβ[redacted], the antibody dependent cellular phagocytosis (ADCP) activity of donanemab was evaluated by a reporter gene assay that measures the expression of [redacted].

2.1.5.2 Product-related substances/Product-related impurities

On the basis of the results of the characterization studies presented in Section “2.1.5.1 Structure and characterization” and other data, Related Substance A, Related Substance B, Related Substance C, Related Substance D, Related Substance E, and Related Substance F were identified as product-related substances. Aggregates, fragments, Impurity A, Impurity B, Impurity C, and Impurity D were identified as product-related impurities. Aggregates, fragments, and Impurity B are controlled by the specifications for the drug substance

and drug product. The past manufacturing records have demonstrated that other product-related impurities are consistently controlled at low levels; therefore, these impurities are not controlled by routine testing.

2.1.5.3 Process-related impurities

Host cell DNA, Impurity E, host cell proteins (HCPs), elemental impurities, Impurity F, Impurity G, Impurity H, and Impurity I were defined as process-related impurities. It has been verified that host cell DNA, Impurity E, elemental impurities, Impurity F, Impurity G, Impurity H, and Impurity I are adequately removed in the manufacturing process. Host cell proteins are controlled by the specifications for the drug substance.

2.1.6 Control of drug substance

The proposed specifications for the drug substance include content, description, identification (cation exchange chromatography, reporter gene assay, peptide mapping), pH, purity (size exclusion chromatography [SEC], capillary electrophoresis-sodium dodecyl sulphate [CE-SDS; non-reducing and reducing conditions], and HCP), bacterial endotoxins, microbial limit, charge heterogeneity (capillary isoelectric focusing [cIEF]), potency (reporter gene assay), and assay (ultraviolet-visible spectrophotometry).

2.1.7 Stability of drug substance

Table 3 shows main stability studies for the drug substance.

Table 3. Summary of main stability studies for the drug substance

		Manufacturing process for drug substance	Number of batches	Storage condition	Study period	Storage form
Long-term		Proposed process	4	≤−65°C	24 months[a]	Polycarbonate container with polypropylene copolymer cap [redacted]
Accelerated		Proposed process	3	2°C to 8°C	12 months	
Stress	Temperature	Previous process	1	40°C	4 weeks	Glass vial
	Light			Overall illumination of 1.2 million lux·h and an integrated near ultraviolet energy of 200 W·h/m^2, at 15°C		

a, The stability test is ongoing up to [redacted] months.

Under the long-term storage condition, no clear changes in quality attributes were shown throughout the test period.

The accelerated stability study showed a trend toward a decrease in monomers and a trend toward an increase in aggregates, as determined by SEC; and a trend toward a decrease in the main peak, as determined by CE-SDS ([redacted]).

The stress (temperature) study showed a decrease in monomers and an increase in aggregates, as determined by SEC; a decrease in the main peak and an increase in fragments, as determined by CE-SDS ([redacted]); a decrease in the main peak, as determined by CE-SDS ([redacted]); and a decrease in the main peak, a trend toward an increase in [redacted] and a trend toward an increase in [redacted], as determined by cIEF.

The stress study (light) showed that the drug substance is photolabile.

Based on the above, a shelf life of 24 months has been proposed for the drug substance when stored at ≤−65°C in a polycarbonate container with a polypropylene copolymer cap [redacted].

2.2 Drug product

2.2.1 Description and composition of drug product and formulation development

The drug product is an aqueous solution for injection supplied in a glass vial (20 mL) containing 350 mg of donanemab. Excipients contained in the drug product are sodium citrate hydrate, anhydrous citric acid, sucrose, polysorbate 80, and water for injection.

2.2.2 Manufacturing process

The manufacturing process for the drug product consists of preparation of excipient buffer solutions, preparation of drug solution, sterile filtration, filling/stoppering/crimping, labeling/packaging/testing, and storage.

[redacted] and [redacted] have been defined as critical steps.

Process validation for the manufacturing process of the drug product is performed on a commercial scale.

2.2.3 Manufacturing process development

Multiple changes were made to the manufacturing process during the development of the drug product, which include a change from Formulation A to the solution formulation. Comparability between pre-change and post-change drug products has been evaluated in accordance with the ICH Q5E guidelines.

2.2.4 Control of drug product

The proposed specifications for the drug product include strength, description, identification (cation chromatography and reporter gene assay), pH, purity (SEC and CE-SDS [non-reducing and reducing conditions]), bacterial endotoxins, extractable volume, foreign insoluble matter, insoluble particulate matter, sterility, charge heterogeneity (cIEF), potency (reporter gene assay), and assay (ultraviolet-visible spectrophotometry).

2.2.5 Stability of drug product

Table 4 shows main stability studies for the drug product.

Table 4. Summary of main stability studies for the drug product

		Manufacturing process for drug product[a]	Number of batches	Storage condition	Study period	Storage form
Long-term		Proposed process	3	2°C to 8°C	24 months[b]	Glass vial with chlorobutyl rubber stopper
Accelerated		Proposed process	3	25°C/60% RH	6 months	
Stress	Light	Previous process	1	Overall illumination of ≥1.2 million lux·h and an integrated near ultraviolet energy of ≥200 W·h/m^2, at 15°C		

a, The manufacturing process for the drug substance is the proposed process.
b, The stability study is ongoing up to [redacted] months.

The long-term storage study showed a trend toward a decrease in monomers and a trend toward an increase in aggregates, as determined by SEC; a trend towards a decrease in the main peak and a trend toward an increase in fragments, as determined by CE-SDS ([redacted]).

The accelerated stability study showed a trend toward a decrease in monomers and a trend toward an increase in aggregates, as determined by SEC; a trend toward a decrease in the main peak and a trend toward an increase in fragments, as determined by CE-SDS ([redacted]); a trend toward a decrease in the main peak, as determined by CE-SDS ([redacted]); and a trend toward a decrease in the main peak and a trend toward an increase in [redacted], as determined by cIEF.

The stress (light) study showed that the drug product is photolabile.

Based on the above, a shelf life of 24 months has been proposed for the drug product when placed in a glass vial with a chlorobutyl rubber stopper as the primary packaging and protected from light in a paper box stored at 2°C to 8°C.

2.3 Quality control strategy

On the basis of the investigations shown below, the applicant developed a strategy to control quality through a combination of process parameters, in-process controls, specifications, and stability studies [for the control of product-related impurities and process-related impurities, see Sections "2.1.5.2 Product-related substances/Product-related impurities" and "2.1.5.3 Process-related impurities," respectively].

- Identification of critical quality attributes (CQAs):
  The following CQAs were identified based on the information obtained through the development of donanemab and related findings.
  CQAs for the drug substance: aggregates, fragments, [redacted], [redacted], [redacted], [redacted], potency, host cell DNA, [redacted], HCP, elemental impurities, [redacted], [redacted], [redacted], [redacted], microbiological safety, virus safety, identification (identity), protein content, [redacted] concentration, pH, description

CQAs for the drug product: aggregates, fragments, [redacted], potency, elemental impurities, microbiological safety, insoluble particulate matter, identification (identity), protein content, osmolality, polysorbate 80 concentration, pH, description, extractable volume

- Process characterization

  Based on information obtained through the development of donanemab, risk assessment, and other findings, steps that have an impact on CQAs were identified, and process parameters that have an impact on the CQAs for the identified steps were also selected. In addition, the acceptable range for the process parameters was determined.

2.R Outline of the review conducted by PMDA

On the basis of the submitted data, PMDA concluded that the quality of the drug substance and drug product is adequately controlled.

3. Non-clinical Pharmacology and Outline of the Review Conducted by PMDA

3.1 Primary pharmacodynamics

3.1.1 *In vitro* studies

3.1.1.1 Binding affinity and selectivity of donanemab and mE8c for $A\beta_{p3-x}$ (CTD 4.2.1.1.1)

The binding affinity of donanemab and mE8c[1)] (0.0625-1 μmol/L for both) for $A\beta_{p3-42}$ and $A\beta_{p3-16}$ was investigated by surface plasmon resonance (SPR). The K_D values[2)] for $A\beta_{p3-42}$ and $A\beta_{p3-16}$ were 0.82 ± 0.05 nmol/L and 3 ± 2 nmol/L, respectively, for donanemab, and <0.2 nmol/L and 0.6 nmol/L, respectively, for mE8c. Likewise, the binding affinity for $A\beta_{1-40}$ was also investigated, and neither donanemab nor mE8c (1 μmol/L for both) showed binding affinity for $A\beta_{1-40}$.

The binding affinity of donanemab and mE8c was evaluated by SPR for the following Aβ peptides: 5 $A\beta_{p3-16}$ species in which the amino acid residue (F4, H6, D7, S8, or Y10) in the binding epitope (position 3 to position 10) for $A\beta_{p3-x}$ was substituted, murine $A\beta_{p3-16}$ (whose amino acid residues are different from amino acid residues, R5 and Y10, in human $A\beta_{p3-16}$), and human $A\beta_{3-16}$ in which amino acid residues in the binding epitope are not pyroglutamate-modified (pE3). The impact of the amino acid residues on the binding affinity of donanemab and mE8c for $A\beta_{p3-x}$ was in the following order: F4 and R5 > pE3 > D7 > H6 > Y10. No impact was observed for S8.

[1)] mE8c is a murine anti-$A\beta_{p3-X}$ antibody (IgG2a isotype), mE8 is a murine anti-$A\beta_{p3-X}$ antibody (IgG1 antibody), and 3D6 is a murine anti-$A\beta_{1-X}$ antibody (IgG2b isotype). These antibodies can bind to soluble Aβ and Aβ in amyloid plaques. The level of effector function in mice was in the following order: mE8 < 3D6 < mE8c.

[2)] The K_D value for donanemab is the mean ± standard deviation of the results from 3 tests, while the K_D value for mE8c is the result from 1 test.

3.1.2 *Ex vivo* studies

3.1.2.1 Binding characteristics of donanemab for amyloid plaques (CTD 4.2.1.1.3)

The binding characteristics of donanemab for amyloid plaques were investigated by immunohistochemical staining using frozen sections of brain tissue from patients with AD. Donanemab bound to amyloid plaques in patients with AD.

3.1.2.2 Effects of mE8 and mE8c on microglial removal of Aβ (CTD 4.2.1.1.2)

After the addition of mE8[1)] or mE8c (0.065 μmol/L) to frozen sections of brain tissue from patients with AD, the primary murine microglia culture was added to the tissue sections. At 24 hours later, $A\beta_{1-42}$ levels in the tissue sections were measured by enzyme-linked immunosorbent assay (ELISA). The results showed that the $A\beta_{1-42}$ levels were significantly lower in tissue sections treated with mE8 or mE8c than in those not treated with either of them. The $A\beta_{1-42}$ levels were significantly lower in tissue sections treated with mE8c than in tissue sections treated with mE8.

3.1.3 *In vivo* studies

3.1.3.1 Binding characteristics of donanemab and mE8 for amyloid plaques in PDAPP mice (CTD 4.2.1.1.4)

Male PDAPP mice[3)] 16 to 19 months of age was given m3D6[1)] or mE8 (40 mg/kg) intraperitoneally once weekly for 4 weeks. The binding characteristics of m3D6 or mE8 for amyloid plaques were evaluated by immunohistochemistry staining 3 days after the last dose. The results showed that m3D6 bound to amyloid plaques along the hippocampal sulcus, while mE8 bound to amyloid plaques in the hippocampus and in all regions of the cortex.

A single dose of donanemab (40 mg/kg) was administered intraperitoneally to female PDAPP mice 19 months of age. The binding characteristics of donanemab for amyloid plaques were evaluated by immunohistochemistry staining 3 days later. Donanemab bound to amyloid plaques in PDAPP mice.

3.1.3.2 Effects of mE8 and mE8c for Aβ in the brain of PDAPP mice (CTD 4.2.1.1.5, 4.2.1.1.8)

Male and female PDAPP mice 23 to 24 months of age (N = 23 to 30/group) were given m3D6, mE8, mE8c, or negative control antibody (IgG2a) (12.5 mg/kg) intraperitonially once weekly for 3 months. The hippocampal and cortical $A\beta_{1-42}$ levels were determined by Western blotting. The $A\beta_{1-42}$ levels of control-treated animals necropsied at the start of the study (0-hour control group) were also evaluated in a similar manner. Hippocampal $A\beta_{1-42}$ levels in the mE8 and mE8c groups were reduced by 38% and 53%, respectively, compared with the control antibody group, and the hippocampal $A\beta_{1-42}$ level in the mE8c group was 30% lower than that in the 0-hour control group. The cortical $A\beta_{1-42}$ levels were significantly lower in the mE8c group than in the antibody control group, while there was no significant difference between the mE8 group and the control antibody group. In the m3D6 group, $A\beta_{1-42}$ levels in the hippocampus and cortex did not differ significantly from those in the control antibody group.

[3)] A mouse model of AD overexpressing mutant human amyloid precursor protein (APP^{V717F}). The transgenic mouse undergoes a region-specific increase in amyloid plaque deposition in the brains at 6 to 18 months of age.

Male and female 5.5-month-old PDAPP mice (N = 29/group) were given m3D6, mE8c, or negative control antibody (IgG2a) (12.5 mg/kg) subcutaneously once weekly for 7 months, and hippocampal $A\beta_{1-42}$ levels were measured by ELISA. The $A\beta_{1-42}$ levels in the 0-hour control group were also evaluated in a similar manner. Hippocampal $A\beta_{1-42}$ levels were hardly detected in the 0-hour control group (5.5 months of age). The hippocampal $A\beta_{1-42}$ levels in the negative control group (12.5 months of age) were approximately 45 times those in the 0-hour control group. Conversely, the hippocampal $A\beta_{1-42}$ levels in the m3D6 group were significantly lower than those in the negative control group. There was no significant difference between the mE8c group and the negative control group.

3.1.3.3 Effects of donanemab and mE8c on soluble Aβ in PDAPP mouse plasma (CTD 4.2.1.1.6)

It has been reported that when binding of anti-Aβ antibodies and soluble Aβ are saturated in blood, plasma $A\beta_{1-40}$ concentrations increase as the result of a change in the equilibrium of Aβ between the central nervous system (CNS) and plasma (*Proc Natl Acad Sci USA.* 2001;98:8850-5). Female PDAPP mice 5 to 7 months of age (N = 4/group) were subcutaneously given donanemab, mE8c, or m266, which strongly binds to soluble Aβ, or the negative control antibody (IgG) (10 mg/kg), and plasma $A\beta_{1-40}$ concentrations at 24 hours post-dose were determined by ELISA. The results showed that plasma $A\beta_{1-40}$ concentrations in the m266 group were approximately 100 times those in the control antibody group, while no clear increase was noted in the donanemab group or mE8c group compared to the control antibody group.

3.2 Safety pharmacology

Table 5 shows the results of safety pharmacology studies.

Table 5. Summary of safety pharmacology studies

Item	Test system	Evaluation parameter/technique	Dose (mg/kg)	Route of administration	Findings	CTD
Central nervous system	Cynomolgus monkey (N = 3 to 6/sex/group)	General behavior, temperature	0,[a] 1, 10, 100	IV	No effects	4.2.3.2.4
Cardiovascular system	Cynomolgus monkey (N = 3 to 6/sex/group)	Heart rate, electrocardiogram (telemetry)	0,[a] 1, 10, 100	IV	No effects	4.2.3.2.4
Respiratory system	Cynomolgus monkey (N = 3 to 6/sex/group)	Respiratory rate, minute ventilation	0,[a] 1, 10, 100	IV	No effects	4.2.3.2.4

a, A solution containing 10 mmol/L sodium citrate, 150 mmol/L sodium chloride, and 0.02% (w/v) polysorbate 80

3.R Outline of the review conducted by PMDA

The applicant's explanation about the mechanism by which donanemab slows the progression of AD:

It has been suggested that anti-Aβ antibody-mediated removal of amyloid plaques invloves binding of the anti-Aβ antibody to amyloid plaques and enhancement of microglial phagocytosis of amyloid plaques (*Nat Rev Neurosci.* 2002;3:824-8). The $A\beta_{p3-x}$ fragment, which is an N-terminally truncated Aβ, missing 2 amino acids and is pyroglutamate-modified, is one type of Aβ fragments found in amyloid plaques in the brain of patients with AD. Molecules recognized by anti-$A\beta_{p3-x}$ antibodies were not detected in cerebrospinal fluid (CSF) or in the soluble fractions of brain extracts from patients with AD, but were detected only in the insoluble fractions of brain extracts (CTD 4.2.1.1.9 [reference data]). The findings suggest that $A\beta_{p3-x}$ is likely to be present

specifically in amyloid plaques. The applicant, therefore, considered that $A\beta_{p3-x}$ could be served as an optimum target molecule in the development of a drug for the treatment of AD intended for the removal of amyloid plaques.

Donanemab, a humanized anti-Aβ monoclonal antibody, was manufactured as an antibody that has a high affinity for $A\beta_{p3-x}$. The *in vitro* studies showed that donanemab and mE8c bound to $A\beta_{p3-42}$, while the *in vivo* studies showed that donanemab and mE8 bound to amyloid plaques from PDAPP mice. In addition, the *ex vivo* studies showed that mE8 and mE8c reduced the level of $A\beta_{1-42}$ in brain tissue sections from patients with AD in the presence of the primary murine microglia culture, and the *in vivo* studies showed that mE8 or mE8c reduced the level of $A\beta_{1-42}$ in the brain of aged PDAPP mice.

The above results suggest that donanemab removes amyloid plaques by binding to $A\beta_{p3-x}$ in amyloid plaques and thereby promoting microglial phagocytosis. Therefore, donanemab is expected to slow the progression of AD symptoms by reducing amyloid plaques.

PMDA's view:
Whether a donanemab-induced reduction in amyloid plaques can contribute to slowing of the progression of AD symptoms cannot be determined based only on non-clinical data. Given the applicant's explanation, however, donanemab can be expected to reduce amyloid plaques also in humans by binding to $A\beta_{p3-x}$ in amyloid plaques.

4. Non-clinical Pharmacokinetics and Outline of the Review Conducted by PMDA

The serum concentrations of donanemab in monkeys were measured by ELISA. The lower limit of quantitation (LLOQ) was 15.6 ng/mL.

Unless otherwise specified, pharmacokinetic (PK) parameters are expressed as mean ± standard deviation.

4.1 Absorption

4.1.1 Single-dose study (CTD 4.2.2.2.1)

Table 6 shows the PK parameters of donanemab following a single intravenous or subcutaneous dose of donanemab in male monkeys.

Table 6. PK parameters following a single intravenous (IV) or subcutaneous (SC) dose of donanemab in monkeys

Dose (mg/kg)	Route of administration	N	C_{max} (μg/mL)	t_{max} (h)	AUC_{0-672h} (μg·h/mL)	$t_{1/2}$ (h)	CL (mL/h/kg)	CL/F (mL/h/kg)	V_{ss} (mL/kg)	BA (%)
1	IV	3	25.2 ± 6.7	—	1860 ± 472	173 ± 53	0.53 ± 0.13	—	85.8 ± 11.7	—
	SC	3	7.6 ± 1.2	64 ± 14	1690 ± 152	161 ± 19	—	0.59 ± 0.05	—	91

"—," Not calculated

4.1.2 Repeated-dose study (CTD 4.2.3.2.4)

Donanemab was intravenously administered to male and female monkeys once weekly for 6 weeks. Table 7 shows the PK parameters of donanemab following repeated intravenous doses of donanemab in the animals.

Table 7. PK parameters of donanemab following once-weekly intravenous doses of donanemab in monkeys

Dose (mg/kg)	N (Male/Female)	Timepoint (Day)	C_{max} (μg/mL)		$AUC_{0\text{-}166h}$ (μg·h/mL)	
			Male	Female	Male	Female
1	3/3	1	17.1 ± 2.66	15.7 ± 2.85	1060 ± 107	1060 ± 95.1
		36	26.5 ± 5.40	24.7 ± 3.77	1950 ± 536	1620 ± 621
10	3/3	1	202 ± 17.2	184 ± 21.1	11000 ± 646	10200 ± 1240
		36	255 ± 13.9	264 ± 20.8	20900 ± 835	17600 ± 2660
100	6/6	1	2270 ± 431	2710 ± 538	87100 ± 7990	94600 ± 15200
		36	2650 ± 798	2540 ± 365	139000 ± 21400	146000 ± 20300

4.2 Distribution

4.2.1 Tissue distribution

No studies on the tissue distribution of donanemab were conducted. The applicant provided the following explanation about the distribution of donanemab:

- Given that the molecular weight of donanemab, an IgG antibody, is approximately 148,000, and that there is no significant difference between the volume of distribution at steady state (V_{ss}) of donanemab (approximately 86 mL/kg) from the single intravenous dose study in monkeys [see Section "4.1.1 Single-dose study"] and the total blood volume in monkey (73.4 mL/kg; *Pharm Res.* 1993;10:1093-5), donanemab, like other IgG antibodies, is distributed in the vascular system.
- Following intravenous administration of donanemab to patients with early AD or moderate AD-D, a certain percentage of donanemab was detected in CSF, indicating that donanemab can enter the brain [see Section "6.2.1.2 Single-dose and multiple-dose study in patients with early AD and moderate AD-D"].

4.2.2 Placental transfer

Although no studies on the placental transfer of donanemab were conducted, there have been studies reporting that IgG crosses the human placenta (*Am J Reprod Immunol.* 1996;36:248-55, *Am J Gastroenterol.* 2009;104:228-33, *Clin Dev Immunol.* 2012;2012:985646). Based on these reports, the applicant asserted that donanemab, an IgG antibody, can also be transported across the placenta into the fetus.

4.3 Metabolism and excretion

While no studies on the metabolism or excretion of donanemab were conducted, the applicant provided the following explanation about the metabolism or excretion of donanemab:

As with other IgG antibodies, donanemab, which is an IgG antibody, is catabolized and degraded into peptides and amino acids. Furthermore, based on the publication reporting that IgG antibodies are excreted into human milk (*J Hum Lact.* 2005;21:439-43), donanemab, an IgG antibody, may also be distributed in breast milk. In view of the above, the package insert will include a cautionary statement to the effect that before administering donanemab, the therapeutic benefits and the benefits of breastfeeding should be assessed to determine whether to continue breastfeeding.

4.R Outline of the review conducted by PMDA

Although no non-clinical pharmacokinetic studies were conducted to evaluate the distribution, metabolism, and excretion of donanemab, the pharmacokinetic properties can be predicted from available data. On the basis of the submitted data and the applicant's explanation, PMDA concluded that the non-clinical pharmacokinetics of donanemab has been adequately evaluated.

5. Toxicity and Outline of the Review Conducted by PMDA

The applicant conducted repeated-dose toxicity studies and other toxicity studies of donanemab (tissue cross reactivity studies, evaluation of microhemorrhage in PDAPP mice). Unless otherwise specified, a solution (pH 6.0) containing 10 mmol/L sodium citrate, 150 mmol/L sodium chloride, and 0.02% (w/v) polysorbate 80 was used as a vehicle.

5.1 Single-dose toxicity

No independent single-dose toxicity studies were conducted. The acute toxicity of donanemab was evaluated based on the data obtained after the first dose in the repeated-dose toxicity study of donanemab in cynomolgus monkeys (Table 8). No acute toxicity or deaths were reported after the first dose.

Table 8. Repeated-dose toxicity study (findings after the first dose)

Test system	Route of administration	Dose (mg/kg)	Major findings	Approximate lethal dose (mg/kg)	CTD
Male/female cynomolgus monkey	IV	0, 1, 10, 100	None	>100	4.2.3.2.4

5.2 Repeated-dose studies

A repeated-dose toxicity study (6 weeks) of donanemab in cynomolgus monkeys and a repeated-dose toxicity study (for a maximum of 6 months) of mE8c in PDAPP mice were conducted (Table 9). No noteworthy toxicological findings were noted in either of the studies. In the repeated-dose toxicity study (6 weeks) of donanemab in cynomolgus monkeys, the exposure ($AUC_{\tau, ss}$) in animals treated at the no-observed adverse effect level (NOAEL), 100 mg/kg, was 142000 μg·hr/mL, and the corrected exposure for the difference in dosing interval was approximately 10.5-fold the clinical exposure ($AUC_{\tau, ss}$).[4)]

[4)] The $AUC_{\tau, ss}$ (54900 μg·hr/mL) in humans following intravenous administration of donanemab 1400 mg every 4 weeks, assuming a body weight of 70 kg. This value was calculated based on the PPK analysis [see Section "6.2.1.3 Population pharmacokinetic analysis"].

Table 9. Summary of repeated-dose toxicity studies

Test system	Route of administration	Dosing period	Dose (mg/kg/dose)	Major findings	NOAEL (mg/kg/dose)	CTD
Male/female cynomolgus monkey	IV	6 weeks (once weekly) + 3-month recovery period	Donanemab: 0, 1, 10, 100	None	100	4.2.3.2.4[c]
Male/female mouse (12-15-month-old PDAPP)	SC	6 weeks (once weekly)	mE8c: 0,[a] 10, 30, 100	Deaths: at 0 (M, 1/10; F, 3/10); at 10 (M, 2/10; F, 3/9); at 30 (M, 2/9); at 100 (M, 2/10)[b]	100	4.2.3.2.3[c]
Male/female mouse (12-15-month-old PDAPP)	SC	Males: 151-152 days (once weekly)[d] Females: 140-141 days (once weekly)[d]	mE8c: 0,[a] 30, 100	Deaths: at 0 (M, 15/20; F, 12/20); at 30 (M, 7/19; F, 11/19); at 100 (M, 10/19; F, 15/19)[b]	100	4.2.3.2.1[c]
Female mouse (16-month-old PDAPP)	SC	6 months (once weekly)	mE8c: 0,[a, e] 1.5, 4, 12.5	Deaths: at 0 (7/30); at 1.5 (6/30); at 4 (7/30); at 12.5 (7/30)[b]	12.5	4.2.3.2.2[c] (Reference data)

[a] Phosphate-buffered saline (PBS) (pH 7.4) was used as a vehicle.
[b] In these animals that died, worsened clinical observations and malignant neoplasm in the blood/lymphatic tissue were noted, and the animals tested were old. Based on these and other factors, the death of these animals was not considered atrtributable to mE8c treatment.
[c] Including the neuropathological assessment of the brain.
[d] Although 6-month treatment was planned, the treatment was discontinued early because some animals died due to aging.
[e] IgG2a antibody at 12.5 mg/kg was administered to animals in the control group.

5.3 Genotoxicity

Donanemab, an IgG antibody, is unlikely to interact directly with DNA or other chromosome components, and therefore no genotoxicity studies were conducted.

5.4 Carcinogenicity

Carcinogenicity studies were not conducted because such studies were considered of little significance for the following reasons: the target of donanemab is present only in amyloid plaques, and it does not exist in rodents used for carcinogenicity studies. The applicant asserted that the carcinogenic risks associated with donanemab are low due to the following factors:

- Given the physiological function of Aβ, the risk of carcinogenesis resulting from the removal of amyloid plaques containing $A\beta_{p3\text{-}x}$, the pharmacological action of donanemab, is expected to be low.
- Donanemab specifically binds to $A\beta_{p3\text{-}x}$, which is present only in amyloid plaques, and is unlikely to exhibit off-target effects.
- Donanemab is not expected to pose genotoxic risks. The non-clinical studies of donanemab showed no findings suggestive of carcinogenicity (e.g., cytotoxicity, inflammation, evidence of hormonal fluctuation, increased tumors, preneoplastic lesions such as tissue hyperplasia, signs of immunomodulatory or immunosuppressive effects).
- In the clinical studies of donanemab, no adverse events indicative of a risk of tumorigenesis were reported.

5.5 Reproductive and developmental toxicity

The target of donanemab is present only in amyloid plaques, and these plaques do not exist in animal species used in reproductive and developmental toxicity studies. Because it is of little significance to conduct

reproductive and developmental toxicity studies, no such studies were conducted. The applicant asserted that the reproductive and developmental toxicity risks associated with donanemab are low due to the following factors:

- Given the physiological function of Aβ, the reproductive and developmental risks associated with the removal of amyloid plaques containing $A\beta_{p3\text{-}x}$, the pharmacological action of donanemab, are likely to be low.
- No findings from the toxicity studies of donanemab and mE8c indicated any effects on reproductive organs.
- In the clinical studies of donanemab, no adverse events suggestive of reproductive and developmental risks associated with the pharmacological action were reported.

Since no reproductive and developmental toxicity studies of donanemab have been conducted, the applicant explained that the package insert would include a cautionary statement to the effect that donanemab may be administered to women who are or may be pregnant only if therapeutic benefits outweigh the risks.

5.6 Local tolerance

The local tolerance of intravenous donanemab was evaluated as part of the repeated-dose toxicity study in cynomolgus monkeys (Table 9). The local irritation potential caused by intravenous administration of donanemab was determined to be low.

5.7 Other toxicity studies

5.7.1 Tissue cross-reactivity studies (CTD 4.2.3.7.7.1)

The cross-reactivity of donanemab (5 or 25 μg/mL) with human or cynomolgus monkey tissue was evaluated. No toxicologically significant donanemab-specific staining was observed in any tissue of either animal species.

5.7.2 Microhemorrhage study

A study was conducted in PDAPP mice to evaluate the ability of anti-$A\beta_{p3\text{-}X}$ antibodies to induce cerebral amyloid angiopathy (CAA)-related microhemorrhage and neurodegenerative changes associated with amyloid plaque reduction (Table 10). In the 3D6 group, which received bapineuzumab,[5)] a murine surrogate antibody used as a positive control, an increase in the number of cerebral microhemorrhages was noted. Conversely, mE8 and mE8c, anti-$A\beta_{p3\text{-}X}$ antibodies, did not cause cerebral microhemorrhages or neurodegenerative changes.

Table 10. Summary of microhemorrhage study

Test system	Method	Major findings	CTD
Male/female mouse (23-24 month-old PDAPP)	After intraperitoneal administration of IgG2a, mE8, mE8c, or 3D6 at 12.5 mg/kg[a] once weekly for 3 months, a neuropathological examination of brain tissue was performed.	No exacerbation of cerebral microhemorrhage was noted in the mE8 and mE8c groups. A significant increase in the number of cerebral microhemorrhages was noted in the 3D6 group. No neurodegenerative changes were noted in any of the groups.	4.2.3.7.7.2 (Reference data)

[a] mE8 (anti-$A\beta_{p3\text{-}X}$ antibody, IgG1), mE8c (anti-$A\beta_{p3\text{-}X}$ antibody, IgG2a), or 3D6 (anti-$A\beta_{1\text{-}X}$ antibody, IgG2b; which was positive control antibody)

[5)] An anti-$A\beta_{1\text{-}X}$ antibody

5.R Outline of the review conducted by PMDA

5.R.1 Cerebral microhemorrhage risks

No cerebral microhemorrhage was observed in the repeated-dose toxicity study of mE8c, a surrogate antibody of donanemab, conducted in PDAPP mice. The applicant performed hazard identification studies on cerebral microhemorrhage associated with donanemab treatment in PDAPP mice. PMDA asked the applicant to explain why the applicant performed the hazard identification studies using PDAPP mice and why microhemorrhage associated with donanemab treatment was not observed in the transgenic mice.

The applicant's explanation:

The applicant decided to perform hazard identification studies on cerebral microhemorrhage associated with donanemab treatment in the test system using PDAPP mice considering the following points:

- The findings shown below suggest that CAA is associated with an underlying mechanism by which an anti-Aβ antibody induces amyloid-related imaging abnormalities (ARIA) and cerebral microhemorrhage:
  - Aged PDAPP mice treated with 3D6 (anti-$A\beta_{1-5}$ antibody) underwent formation of an immunocomplex of the anti-Aβ antibody and CAA, followed by activation of perivascular macrophages, leading to plasma protein extravasation and cerebral microhemorrhage (*Mol Neurodegener.* 2023;18:59).
  - In aged amyloid precursor protein (APP) transgenic mice (APP23), the occurrence of CAA results in central nervous system vascular disorders, and administration of an anti-Aβ antibody in the presence of CAA induces cerebral microhemorrhage (*J Neurosci.* 2001;21:1619-27, *Science.* 2002;298:1379).
  - The postmortem findings in the clinical study on active immunotherapy with AN1792[6)] suggest that vascular damage can occur due to an increase in CAA associated with the use of AN1792 and subsequent exacerbation of CAA (*Acta Neuropathol.* 2010;120:369-84). As an underlying mechanism of increasing CAA, overloading of perivascular drainage pathways caused by an increase in soluble Aβ mediated by the promotion of Aβ plaque removal has been reported (*Alzheimers Dement.* 2013;9:S105-15, *Nat Rev Neurol.* 2020;16:30-42).
  - Some patients with CAA present with CAA-related inflammation with radiographical, neuropathological findings similar to ARIA observed in patients with AD treated with an anti-Aβ antibody (*Neurology.* 2007;68:1411-6).
- CAA is shown to occur in PDAPP mice aged ≥21 months, and its severity is known to increase with age (*J Neurosci.* 2005;25:629-36).

The applicant presumed the reason why microhemorrhage was not observed in mice treated with mE8c in the non-clinical study in PDAPP mice and explained it in the following way:

The composition of $A\beta_{p3-x}$, the target molecule of donanemab and mE8c, present in CAA was analyzed. While the composition of $A\beta_{p3-x}$ present in CAA in patients with AD (0.9%) is comparable to that in 30-month-old PDAPP mice (2.1%), molecular species of $A\beta_{p3-x}$ vary, with more $A\beta_{p3-40}$ present in patients with AD and more $A\beta_{p3-42}$ present in PDAPP mice. In addition, there was a difference in the main Aβ molecular species comprising CAA. While $A\beta_{x-40}$ accounts for 95.7% in patients with AD, in PDAPP mice, $A\beta_{x-42}$ accounts for

6) $A\beta_{1-42}$ and adjuvant

62.6%, followed by $A\beta_{x-40}$, which accounts for 37.6%. Aβ truncation, pyroglutamate modification, and C-terminal heterogeneity are known to be involved in aggregation in a mutually independent manner, and $A\beta_{p3-42}$ has shown an increasing trend toward aggregation compared to $A\beta_{p3-40}$ (*Biochemistry*. 2006;45:12393-9). Based on the above, the difference in CAA structure between patients with AD and PDAPP mice may have resulted in the occurrence of epitope shielding and/or inadequate local epitope density in PDAPP mice. These factors may possibly have prevented the localization of inflammatory cells sufficient to induce microhemorrhage.

PMDA's view:
Although the reason why no cerebral microhemorrhage was observed in PDAPP mice treated with mE8c in the toxicity study is unclear, it is true that the risk of cerebral microhemorrhage have not been evaluated in the toxicity studies. Therefore, the risk of developing amyloid related imaging abnormalities-hemorrhage or superficial siderosis (ARIA-H) associated with the used of donanemab and the necessity of cautionary statements on this risk will be further discussed in Section "7.R.4 Safety" in view of the clinical study results.

6. Summary of Biopharmaceutic Studies and Associated Analytical Methods, Clinical Pharmacology, and Outline of the Review Conducted by PMDA

6.1 Summary of biopharmaceutic studies and associated analytical methods

Formulation A was used in Study AACG, a foreign phase II study in patients with early AD with low-medium tau levels in the brain. Formulation A and a solution formulation were used in Study AACI, a global phase III study that was conducted in patients with early AD with low to high tau levels in the brain. The to-be-marketed formulation is a solution formulation, and Formulation A and the solution formulation has been shown to be comparable in terms of quality [see Sections "2.1.4 Manufacturing process development" and "2.2.3 Manufacturing process development"].

The serum and CSF concentrations of donanemab were measured by ELISA, with the LLOQs being 100 to 200 ng/mL (serum) and 5 ng/mL (CSF).

Donanemab anti-drug antibodies (ADA) and neutralizing antibodies in serum were measured by electrochemiluminescence (ECL), with the LLOQ being 2 ng/mL.

6.2 Clinical pharmacology

6.2.1 Investigations in patients

6.2.1.1 Single-dose and multiple-dose studies in patients with early AD and moderate AD-D (Study AACC, CTD 5.3.3.2.1 [May 2013 to August 2016])

A single dose of donanemab at 0.1, 0.3, 1, 3, or 10 mg/kg was administered to Japanese and non-Japanese patients with early AD and moderate AD-D as an intravenous infusion over 30 to 60 minutes, a single subcutaneous dose of donanemab at 3 mg/kg was administered to Japanese and non-Japanese patients with mild AD and moderate AD-D, or a single intravenous dose of 1 mg/kg was administered to healthy non-Japanese volunteers. Table 11 summarizes the PK parameters of donanemab.

Among patients who had received a single intravenous dose of donanemab, those who were ADA positive[7)] were as follows: 4 of 4 subjects in the 0.1 mg/kg group, 7 of 7 subjects in the 0.3 mg/kg group, 9 of 9 subjects in the 1 mg/kg group, 10 of 11 subjects in the 3 mg/kg group, and 6 of 6 subjects in the10 mg/kg group. Among patients who had received a single subcutaneous dose of donanemab 3 mg/kg, 8 of 8 subjects were ADA positive.[7)] Among healthy volunteers who had received a single intravenous dose of 1 mg/kg of donanemab, 6 of 6 subjects were ADA positive.[7)] Neutralizing antibodies were not measured.

Table 11. PK parameters of donanemab in serum after administration of a single dose of donanemab

Subjects	Dose (mg/kg)	Route if administration	N	C_{max} (μg/mL)	t_{max}[a] (h)	$AUC_{0\text{-}inf}$ (μg·h/mL)	$t_{1/2}$ (h)	CL[b] (L/h)	V_z[b] (L)
Patients	0.1	IV	4	2.90 (35)	1.75 [0.50, 24.00]	191 (32)	54.2 (37)	0.0310 (37)	2.42 (59)
	0.3	IV	7	5.99 (77)	0.50 [0.50, 72.00]	632 (33)	111 (63)	0.0305 (34)	4.89 (69)
	1	IV	9	21.7 (21)	0.50 [0.50, 3.27]	1920 (26)	116 (58)	0.0321 (32)	5.39 (56)
	3	IV	11	71.6 (24)	0.50 [0.50, 24.80]	6320 (19)	130 (55)	0.0318 (33)	5.95 (60)
	3	SC	8	12.0 (34)	120.0 [70.1, 336.0]	3780 (41)	179 (40)	0.0269 (58)	6.96 (56)
	10	IV	6	218 (16)	3.00 [0.50, 3.00]	27400 (39)	251 (50)	0.0260 (25)	9.41 (44)
Healthy volunteers	1	IV	6	31.5 (29)	0.50 [0.50, 3.00]	2200 (17)	76.5 (24)	0.0355 (27)	3.92 (32)

Geometric mean (coefficient of variation, %)
[a] Median [Min, Max]
[b] CL/F and V_z/F were calculated for subcutaneous injection.

6.2.1.2 Single-dose and multiple-dose study in patients with early AD and moderate AD-D (Study AACD, CTD 5.3.3.2.2 [December 2015 to [redacted] 20[redacted]])

A single dose of donanemab was administered to Japanese and non-Japanese patients with early AD and moderate AD-D as an intravenous infusion over ≥1 hour for 10 mg/kg, ≥1.5 hours for 20 mg/kg, or ≥2 hours for 40 mg/kg. The PK parameters of donanemab are shown in Table 12 and CSF donanemab concentrations are shown in Table 13.

Six subjects in the 10 mg/kg group, 7 subjects in the 20 mg/kg group, and 4 subjects in the 40 mg/kg group were ADA positive,[7)] and all these subjects were positive for neutralizing antibodies.

[7)] Subjects in whom ADA had not been detected at baseline and the titer increased to twice the minimum dilution factor or higher after treatment with donanemab; and subjects in whom ADA was detected at baseline andthe titer increased to ≥4-fold the baseline level after treatment with donanemab.

Table 12. PK parameters of donanemab in serum after administration of a single intravenous dose of donanemab

Dose (mg/kg)	Subjects	N	C_{max} (μg/mL)	t_{max}[a] (h)	$AUC_{0\text{-}inf}$ (μg·h/mL)	$t_{1/2}$ (h)	CL (L/h)	V_z (L)
10	Japanese	2	145, 206[b]	1.28, 3.10[b]	32700, 20500[b]	341, 334[b]	0.0122, 0.0292[b]	6.02, 14.1[b]
	Non-Japanese	5	207 ± 26.3	2.07 [2.05, 3.20]	26600 ± 4280	231 ± 87.5	0.0314 ± 0.0100	10.7 ± 5.74
20	Japanese	1	383[b]	1.97[b]	48800[b]	160[b]	0.0184[b]	4.25[b]
	Non-Japanese	6	424 ± 75.1	2.53 [1.78, 3.02]	63400 ± 9760	255 ± 101	0.0250 ± 0.00240	9.00 ± 3.05
40	Japanese	2	919, 804[b]	2.62, 3.18[b]	98400, 84900[b]	174, 162[b]	0.0224, 0.0212[b]	5.60, 4.96[b]
	Non-Japanese	2	832, 1110[b]	3.22, 2.47[b]	113000, 167000[b]	206, 271[b]	0.0265, 0.0191[b]	7.88, 7.48[b]

Mean ± standard deviation
[a] Median [Min, Max]
[b] Individual values (N = 1 or 2)

Table 13. Donanemab concentrations in CSF after administration of a single intravenous dose of donanemab

Dose (mg/kg)	Timepoint (Day)[a]	N	CSF concentration (ng/mL)
10	4	5	124 (45)
20	4	5	405 (16)
40	4	3	767 (51)

Geometric mean (coefficient of variation, %)
[a] In the majority of subjects, CSF was sampled approximately 72 hours after administration of donanemab.

Japanese and non-Japanese patients with early AD or moderate AD-D received donanemab 10 mg/kg every 2 weeks (13 doses in total), or donanemab 10 or 20 mg/kg every 4 weeks (up to 19 doses) as an intravenous infusion. The PK parameters of donanemab are shown in Table 14 and CSF donanemab concentrations are shown in Table 15.

Ten subjects in the 10 mg/kg Q2W group, 8 subjects in the 10 mg/kg Q4W group, and 10 subjects in the 20 mg/kg Q4W group were ADA positive, and all these subjects were positive for neutralizing antibodies.

Table 14. PK parameters of donanemab in serum after administration of multiple intravenous doses of donanemab

Dose (mg/kg)	Subjects	N	Timepoint (Day)	C_{max} (μg/mL)	t_{max}[a] (h)	AUC[b] (μg·h/mL)	$t_{1/2}$ (h)	CL (L/h)	V_{ss} (L)
10 (Q2W)	Japanese	3	1	227 ± 19.4	1.38 [1.32, 3.05]	23100 ± 3710	116 ± 5.76	0.0280 ± 0.00533	4.68 ± 0.984
		2	127	247, 278[c]	1.32, 1.32[c]	8580, 29000[c]	40.0, 136[c]	0.0816, 0.0207[c]	4.01, 3.83[c]
	Non-Japanese	7	1	197 ± 91.0	1.45 [1.12, 3.00]	26300 ± 11800	138 ± 23.9	0.0598 ± 0.0913	12.4 ± 19.8
		5	127	285 ± 75.2	1.58 [1.07, 3.07]	40000 ± 12600	176 ± 29.9	0.0213 ± 0.00801	5.24 ± 2.06
10 (Q4W)	Japanese	3	1	186 ± 24.8	1.35 [1.30, 1.45]	23500 ± 757	172 ± 43.1	0.0220 ± 0.00259	5.38 ± 0.959
		2	141	236, 269[c]	1.33, 1.35[c]	36400, 14100[c]	210, 50.8[c]	0.0151, 0.0355[c]	4.40, 2.36[c]
	Non-Japanese	5	1	308 ± 55.0	3.27 [3.00, 3.43]	47800 ± 9270	220 ± 62.1	0.0166 ± 0.00367	5.05 ± 0.721
		3	141	486 ± 147	1.50 [1.38, 3.03]	49400 ± 10900	202 ± 50.9	0.0163 ± 0.00560	4.16 ± 0.407
20 (Q4W)	Japanese	2	1	453, 391[c]	3.05, 3.05[c]	45300, 67700[c]	195, 235[c]	0.0221, 0.0177[c]	6.22, 6.02[c]
		2	141	513, 415[c]	3.00, 3.00[c]	73400, 81300[c]	211, 250[c]	0.0136, 0.0135[c]	3.64, 4.70[c]
	Non-Japanese	8	1	622 ± 154	2.16 [1.90, 3.32]	68700 ± 17000	204 ± 62.7	0.0242 ± 0.00498	6.97 ± 1.68
		5	141	670 ± 107	1.92 [1.60, 25.05]	68900 ± 28100[d]	134 ± 94.1[d]	0.0256 ± 0.0140[d]	3.67 ± 1.57[d]

Mean ± standard deviation
[a] Median [Min, Max]
[b] $AUC_{0\text{-}inf}$ (Day 1), AUC_{τ} (Days 127 and 141)
[c] Individual values (N = 2)
[d] N = 4

Table 15. Donanemab concentrations in CSF after administration of multiple intravenous doses of donanemab

Dose (mg/kg)	Timepoint (Day)[a]	N	CSF concentration (ng/mL)
10 (Q2W)	169	3	429 (10)
10 (Q4W)	169	5	189 (11)
20 (Q4W)	169	6	293 (57)

Geometric mean (coefficient of variation, %)
[a] In the majority of subjects, CSF was sampled approximately 72 hours after administration of donanemab.

6.2.1.3 Population pharmacokinetic analysis (CTD 5.3.3.5.2 [Reference data])

A population pharmacokinetic (PPK) analysis was performed (NONMEM Version 7.5.0) on serum donanemab concentration data in patients with AD (2,131 subjects; 22,288 timepoints) from the global phase I study (Study AACD), foreign phase II studies (Studies AACG and AACH), and global phase III studies (Study AACI and Study AACI Addendum 9).

The subject characteristics for the PPK analysis were as follows: sex, 960 males and 1,171 females; race, 1,916 subjects (Caucasian), 62 subjects (Black), 135 subjects (Asian), 18 subjects (other race); hepatic impairment classification,[8)] 2,026 subjects (normal hepatic function), 95 subjects (mild hepatic impairment), 6 subjects (moderate hepatic impairment); renal impairment classification,[9)] 347 subjects (normal renal function), 1,021

[8)] Normal = total bilirubin and aspartate aminotransferase (AST) are at the upper limits of normal (ULN) or below; mild = total bilirubin is at ULN or below and AST is above ULN, or total bilirubin is above ULN to 1.5 × ULN; moderate = total bilirubin is above 1.5 × ULN to 3 × ULN; severe = total bilirubin is above 3 × ULN.
[9)] Normal = CrCL ≥90 mL/min; mild = CrCL ≥60 mL/min and <90 mL/min; moderate = CrCL ≥30 mL/min and <60 mL/min; severe = ≥15 mL/min and <30 mL/min.

subjects (mild renal impairment), 741 subjects (moderate renal impairment), 20 subjects (severe renal impairment); apolipoprotein E ε4 (ApoE ε4) carrier status, 302 subjects (homozygous), 1,112 subjects (heterozygous), 707 subjects (non-carrier), 10 subjects (unknown); age, 74.0 years [54, 88] (mean [Min, Max]; the same applies hereinafter); body weight, 73.8 kg [31.8, 157.0]; and post-baseline ADA titer, 160 [1, 5242880]. All of these factors were candidate covariates for PK parameters, i.e., total body clearance (CL), inter-compartment clearance (Q), central volume of distribution (V_c), and peripheral volume of distribution (V_p).

The PK of donanemab was described by a 2-compartment model. Allometric scaling was applied to CL, Q, V_c, and V_p based on body weight (72 kg standard body weight), with allometric coefficient of 0.8 for CL and Q, and 1.0 for V_c and V_p. In the final model, ADA titer was selected as a covariate that has a significant effect on CL.

The estimated population mean of the PK parameters for the final model was 0.0255 L/h (CL), 3.36 L (V_c), 4.83 L (V_p), and 0.0200 L/h (Q), with intra-individual difference being 24.9% (CL), 18.7% (V_c), and 93.9% (V_p).

Using estimated parameters obtained from the final model, the following simulation was performed.

The PK parameters of donanemab were estimated for intravenous administration of donanemab 20 mg/kg (10 mg/kg for the first 3 doses) every 4 weeks, or donanemab 1400 mg (700 mg for the first 3 doses) every 4 weeks. Table 16 shows estimated PK parameters of donanemab at steady state. Table 17 shows estimated PK parameters of donanemab after intravenous administration of donanemab 1400 mg every 4 weeks to Japanese and non-Japanese subjects from Studies AACD, AACG, AACH, and AACI.

Table 16. Estimated PK parameters of donanemab at steady state after administration of body weight-adjusted dose vs. fixed dose

Dosage regimen of donanemab	$AUC_{\tau, ss}$ (μg·h/mL)	$C_{max, ss}$ (μg/mL)	$C_{min, ss}$ (μg/mL)
1400 mg (700 mg for the first 3 doses) IV every 4 weeks	45400 ± 16100	453 ± 135	15.2 ± 11.2
20 mg/kg (10 mg/kg for the first 3 doses) IV every 4 weeks	45300 ± 13000	449 ± 81.5	15.4 ± 10.9

Mean ± standard deviation

Table 17. Estimated PK parameters of donanemab in Japanese and non-Japanese subjects from Studies AACD, AACG, AACH, and AACI

	N	$AUC_{\tau, ss}$ (μg·h/mL)	$C_{max, ss}$ (μg/mL)	$C_{min, ss}$ (μg/mL)
Japanese	115	113000 ± 31500	566 ± 92.9	17.9 ± 12.6
Non-Japanese	2016	87900 ± 28700	432 ± 99.4	15.8 ± 11.9

Mean ± standard deviation

6.2.2 Intrinsic factors

6.2.2.1 Effects of hepatic impairment and renal impairment on donanemab PK

The applicant's explanation:

No clinical pharmacology studies of donanemab in patients with hepatic impairment or renal impairment were conducted. However, given that donanemab is a humanized IgG monoclonal antibody, as with other endogenous IgG antibodies, donanemab is not metabolized by liver drug-metabolizing enzymes, but is broken down into peptides and amino acids by catabolism. Since donanemab is not excreted from the kidney as an unchanged compound, decreased kidney or liver function is unlikely to affect the PK of donanemab.

6.R Outline of the review conducted by PMDA

6.R.1 Differences in PK between Japanese and non-Japanese populations

The applicant's explanation about the differences in the PK of donanemab between Japanese and non-Japanese populations:

On the basis of the results from the global phase I study (Study AACD), the differences in PK between Japanese and non-Japanese populations after a single dose of donanemab 10, 20, or 40 mg/kg (Table 12), multiple doses of donanemab 10 mg/kg every 2 weeks, and multiple doses of donanemab 10 or 20 mg/kg every 4 weeks (Table 14) were investigated. The PK (C_{max}, AUC) in the Japanese population was similar to that in the non-Japanese population after administration of a single dose or multiple doses.

The results of simulation with the PPK analysis using data from the global phase I study (Study AACD), foreign phase II studies (Studies AACG and AACH), and global phase III studies (Study AACI and Study AACI Addendum 9) [see Section "6.2.1.3 Population pharmacokinetic analysis"] showed that the PK after intravenous administration of donanemab 1400 mg every 4 weeks did not differ markedly between Japanese and non-Japanese subjects.

Based on the above, the applicant considrers that there are no clinically relevant differences in the PK of donanemab at the proposed dosage regimen between Japanese and non-Japanese populations.

PMDA concluded that the applicant's explanation (there are no clear differences in the PK of donanemab between Japanese and non-Japanese populations) is reasonable.

6.R.2 ADA

The applicant's explanation about the occurrence of ADA and neutralizing antibodies in the clinical studies:

Table 18 shows the proportion of ADA-positive[7)] subjects in the donanemab group in Studies AACG and AACI and the proportion of ADA-positive subjects who tested positive for neutralizing antibodies.

Table 18. Proportion of ADA-positive[7)] subjects in the donanemab group in Studies AACG and AACI (double-blind period) and proportion of ADA-positive subjects who tested positive for neutralizing antibodies

Study	Donanemab group	
	ADA-positive	Neutralizing antibody-positive[a]
AACG	92.2 (119/129)	100 (119/119)
AACI (double-blind period)	87.4 (693/793)	100 (693/693)

% (n/N)
[a] The denominator is the number of ADA-positive subjects

The serum trough concentrations of donanemab (median ± standard error) in the ADA-positive group and ADA-negative group were 12.0 ± 0.364 μg/mL and 29.2 ± 1.30 μg/mL, respectively, at Week 24; 14.0 ± 0.572 μg/mL and 28.7 ± 0.927 μg/mL, respectively, at Week 52; and 14.5 ± 1.13 μg/mL and 19.7 ± 1.71 μg/mL, respectively, at Week 76; indicating that the presence of ADA tended to decrease serum trough concentrations. However, the change from baseline in amyloid plaque levels at Week 76 in the ADA-positive group and ADA-negative group was −85.15 ± 1.11 and −96.45 ± 2.79, respectively; the change from baseline in Integrated Alzheimer's Disease Rating Scale (iADRS) (least squares mean ± standard error) was −9.28 ± 0.58 and −8.74 ± 1.58, respectively; and the change from baseline in Clinical Dementia Rating-Sum of Boxes (CDR-SB) was 1.56 ± 0.10 and 1.36 ± 0.27, respectively. These results show no marked difference between the groups in terms of the pharmacodynamics (PD) and efficacy of donanemab.

In the pooled data from Study AACG, Study AACH Part B, Study AACI (double-blind and extension periods), Study AACI Addendum 9, and Study AACN (foreign phase III study), the incidence of infusion related reaction in the donanemab group was 10.4% (182 of 1,752 subjects) in the ADA-positive group, which is higher than that in the ADA-negative group, 0.4% (1 of 235 subjects).

PMDA's view:
In the clinical studies, while donanemab exposures tended to decrease in the ADA-positive group compared to the ADA-negative group, there were no clear differences in the PD or efficacy of donanemab between the groups. Safety-related data show that the incidence of infusion related reaction was higher in the ADA-positive group than in the ADA-negative group. However, in Studies AACG and AACI, in which the majority of subjects were ADA positive, adverse events that are possibly related to ADA, i.e., hypersensitivity, anaphylactic reaction, and infusion related reaction, were mild or moderate in severity; and, it is difficult to take measures to prevent ADA-related adverse events [see Section "7.R.4.3 Hypersensitivity, anaphylactic reaction, and infusion related reaction"]. Therefore, it is less meaningful to measure ADA during treatment with donanemab, and the applicant should provide information on the incidence of ADA and neutralizing antibodies in the clinical studies by including it in the package insert.

7. Clinical Efficacy and Safety and Outline of the Review Conducted by PMDA

The applicant submitted efficacy and safety evaluation data, in the form of results data from 5 studies summarized in Table 19 [for PK, see Section "6. Summary of Biopharmaceutic Studies and Associated Analytical Methods, Clinical Pharmacology, and Outline of the Review Conducted by PMDA"].

Table 19. Outline of main clinical studies

Data	Location	Study ID	Phase	Study population	Number of subjects enrolled	Summary of dosage regimen	Main endpoints
Evaluation	Global	AACC	I	Patients with early AD and moderate AD-D, healthy adults (Cohort 7 only)	63	Cohorts 1 to 5: single or multiple intravenous doses of placebo, or donanemab 0.1, 0.3, 1, 3, or 10 mg/kg every 4 weeks for up to 4 doses Cohort 6: a single subcutaneous dose of donanemab 3 mg/kg Cohort 7: a single intravenous dose of donanemab 1 mg/kg	Safety PK
		AACD	Ib	Patients with early AD and moderate AD-D	61	Cohorts 1, 2, and 3: a single intravenous dose of placebo, or donanemab 10, 20, or 40 mg/kg Cohort 4: intravenous doses of placebo or donanemab 10 mg/kg every 2 weeks for 24 weeks Cohort 5[a]: intravenous doses of placebo or donanemab 20 mg/kg every 2 weeks for 24 weeks Cohorts 6 and 7: intravenous doses of placebo, or donanemab 10 or 20 mg/kg every 4 weeks for up to 72 weeks	Safety PK PD
	Foreign	AACG	II	Patients with early AD with low-medium tau level in the brain	272	Intravenous doses of placebo or donanemab 1400 mg (700 mg for the first 3 doses) every 4 weeks for up to 72 weeks. Subjects in the donanemab group were to receive either placebo or β-secretase inhibitor (LY3202626)[b] orally once daily. Subjects whose amyloid plaque reduction as measured by amyloid PET scans at Week 24 or 52 met the criteria[c] are to receive a reduced dose of donanemab (700 mg) or placebo.	Efficacy Safety
	Global	AACI	III[d]	Patients with early AD with a low to high tau level in the brain	1736	**Double-blind period** Intravenous doses of placebo or donanemab 1400 mg (700 mg for the first 3 doses) every 4 weeks up to 72 weeks.[e] Subjects whose amyloid plaque reduction as measured by amyloid PET scans at Weeks 24, 52, or 76 met the dose cessation criteria[f] are to switch to placebo. **Extension period** Subjects whose amyloid plaque reduction as measured by amyloid PET scans at Week 76 met the dose cessation criteria[f] are to receive placebo, and those whose amyloid plaque reduction failed to meet the criteria are to receive donanemab 1400 mg (700 mg for the first 3 doses in subjects who had been in the placebo group in the double-blind period) every 4 weeks for 76 weeks. If amyloid plaque reduction as measured by amyloid PET scans at Week 102 or 130 met the dose cessation criteria,[f] the subjects are to be switched to placebo.	Efficacy Safety
		AACI Addendum 9	III	Patients with early AD	1047	Intravenous doses of donanemab 1400 mg (700 mg for the first 3 doses) every 4 weeks for up to 72 weeks. Donanemab is to be discontinued in subjects whose amyloid plaque levels decreased at Week 24 or 52.	Safety PK

[a] Randomization was not performed.
b According to the Protocol Amendment (d) (dated on October 9, 2018), LY3202626 was no longer coadministered, and subjects were allowed to continue treatment with intravenous donanemab alone.
[c] Subjects whose amyloid plaque level was <11 Centiloids on a single PET scan were to switch to placebo, and subjects whose amyloid plaque level was ≥11 and <25 Centiloids on 2 consecutive PET scans were to receive a reduced dose of donanemab (700 mg).
[d] According to the Protocol Amendment (b) (dated on February 17, 2021), the study was changed from a phase II study to a confirmatory study (phase III).
[e] When the study was initiated, the dosage regimen was intravenous doses of placebo or donanemab 1400 mg every 4 weeks. Early in the study treatment (by Dose 3), serious ARIA-E was reported in 2 subjects. Therefore, according to Protocol Amendment (a), the treatment plan was modified to administer 700 mg for the first 3 doses.
[f] Subjects whose amyloid level was <11 Centiloids on a single PET scan or ≥11 and <25 Centiloids on 2 consecutive PET scans.

7.1 Global phase I study (Study AACC, CTD 5.3.3.2.1 [May 2013 to August 2016])

A randomized study[10)] (Cohorts 1 through 5) and an open-label study (Cohort 6) were conducted in Japanese and non-Japanese patients with early AD or moderate AD-D, and an open-label study (Cohort 7) was conducted in healthy non-Japanese adults at 6 study centers in and outside Japan to investigate the safety, tolerability, and

10) A subject- and rater-blinded study

PK of donanemab (target sample size of up to 100 subjects [including 14 to 22 Japanese subjects in Cohorts 1 through 6, and 6 subjects in Cohort 7]).

Subjects in Cohorts 1 through 5 received a single intravenous dose of placebo, or donanemab 0.1, 0.3, 1, 3, or 10 mg/kg, and after a 12-week follow-up period, received intravenous doses of donanemab every 4 weeks for up to 4 doses.[11)] Subjects in Cohort 6 received a single subcutaneous dose of donanemab 3 mg/kg. Subjects in Cohort 7 received a single intravenous dose of donanemab 1 mg/kg.

Key eligibility criteria for Cohorts 1 through 6

Patients with early AD or moderate AD-D aged ≥50 years who met the following conditions:

- Memory impairment at screening as assessed by Free and Cued Selective Reminding Test with Immediate Recall (FCSRT-IR)
- A Clinical Dementia Rating (CDR) score ≥0.5 and ≤2, and a Memory Box score of ≥0.5 at screening
- A Mini-Mental State Examination (MMSE) score ≥16 and ≤30 at screening
- A positive amyloid positron emission tomography (PET) using florbetapir ^{18}F at screening
- Magnetic resonance imaging (MRI) scans at screening did not show the following findings:
  - Five or more cerebral microhemorrhages
  - Superficial siderosis
  - Findings suggestive of medical history of any cerebral hemorrhage

Key eligibility criteria for Cohort 7

Men aged ≥18 years and ≤40 years who met the following condition:

- The MRI scans at screening did not show the following:
  - Five or more cerebral microhemorrhages
  - Superficial siderosis
  - Findings suggestive of medical history of any cerebral hemorrhage

All of the 63 randomized subjects (Table 20) received the study drug, and were included in the safety analysis set. Five subjects were discontinued from the study in the donanemab group, with the reasons being "withdrawal of consent" (2 subjects), "sponsor's decision" (2 subjects), and "adverse events" (1 subject).

[11)] In Cohort 1, subjects received donanemab 0.1 mg/kg in the SAD period before receiving donanemab 0.3 mg/kg in the MAD period.

Table 20. Subjects disposition

	Cohorts 1 to 5						Cohort 6	Cohort 7
	Patients with early AD or moderate AD-D							Healthy adults
	Single and multiple intravenous doses						Single subcutaneous dose	Single intravenous dose
	Placebo	Donanemab						
		0.1 mg/kg	0.3 mg/kg	1 mg/kg	3 mg/kg	10 mg/kg	3 mg/kg	1 mg/kg
Japanese	5 subjects	2 subjects	3 subjects	3 subjects	4 subjects	2 subjects	2 subjects	0 subjects
Non-Japanese	7 subjects	2 subjects	4 subjects	6 subjects	7 subjects	4 subjects	6 subjects	6 subjects

The incidence of adverse events in patients with early AD or moderate AD-D receiving a single dose was as follows: 58.3% (7 of 12 subjects [including 4 of 5 Japanese subjects]) in the placebo group, 25.0% (1 of 4 subjects [including 1 of 2 Japanese subjects]) in the donanemab 0.1 mg/kg group, 28.6% (2 of 7 subjects) in the donanemab 0.3 mg/kg group, 44.4% (4 of 9 subjects) in the donanemab 1 mg/kg group, 36.4% (4 of 11 subjects) in the donanemab 3 mg/kg group, 16.7% (1 of 6 subjects) in the donanemab 10 mg/kg group, and 50.0% (4 of 8 subjects [including 1 of 2 Japanese subjects]) in the donanemab 3 mg/kg (subcutaneous) group. The incidence of adverse events in healthy adults receiving a single dose was 50.0% (3 of 6 subjects) in the donanemab 1 mg/kg group. Adverse events occurring in ≥2 subjects in any group were upper respiratory tract inflammation in 2 subjects (both were Japanese) in the placebo group. The incidence of adverse events in patients with early AD or moderate AD-D receiving multiple doses was 33.3% (4 of 12 subjects [including 2 of 5 Japanese subjects]) in the placebo group, 54.5% (6 of 11 subjects [including 4 of 5 Japanese subjects]) in the donanemab 0.3 mg/kg group, 44.4% (4 of 9 subjects [including 1 of 3 Japanese subjects]) in the donanemab 1 mg/kg group, 50.0% (4 of 8 subjects [including 2 of 3 Japanese subjects]) in the donanemab 3 mg/kg group, 16.7% (1 of 6 subjects) in the donanemab 10 mg/kg group. Adverse events occurring in ≥2 subjects in any group were infusion related reaction (0 subjects [placebo], 1 Japanese subject [0.3 mg/kg], 2 subjects [1 mg/kg], 3 subjects, including 2 Japanese subjects [3 mg/kg], and 0 subjects [10 mg/kg]).

There were no reports of deaths. Serious adverse events occurred in 1 subject (non-cardiac chest pain) in the placebo group, 1 subject (hip fracture) in the donanemab 0.3 mg/kg (single dose) group, 1 subject (urinary tract infection) in the 0.3 mg/kg (multiple doses) group, and 1 subject (cervical vertebral fracture) in the 1 mg/kg (multiple doses) group. A causal relationship to the study drug was ruled out for all events. An adverse event led to study treatment discontinuation in 1 subject (infusion related reaction) in the 3 mg/kg (multiple doses) group.

7.2 Global phase Ib study (Study AACD, CTD 5.3.3.2.2 [December 2015 to [redacted] 20[redacted]])

A randomized, subject- and rater-blinded study was conducted in Japanese and non-Japanese patients with early AD or moderate AD-D at 8 study centers in and outside Japan to investigate the PD, safety, and PK of donanemab (target sample size, 150 subjects [2 to 3 Japanese subjects/cohort]).

Subjects were to receive a single intravenous dose of placebo, or donanemab 10, 20, or 40 mg/kg in Part A; intravenous doses of placebo, or donanemab 10 or 20 mg every 2 weeks (13 doses in total) in Part B; and intravenous doses of placebo, or donanemab 10 or 20 mg every 4 weeks for up to 19 doses in Part C.

Key eligibility criteria were similar to those employed in Study AACC [see Section "7.1 Global phase I study"].

All of the 61 randomized subjects (Table 21) received the study drug, and were included in the safety analysis set and the full analysis set (FAS). The FAS was the population for the primary PD analysis. A total of 15 subjects discontinued from the study (2 subjects in the placebo group and 13 subjects in the donanemab group), with common reasons for discontinuation being "physician's decision" (0 subjects in the placebo group and 6 subjects in the donanemab group) and "consent withdrawal" (1 subject in the placebo group and 4 subjects in the donanemab group).

Table 21. Subjects disposition

	Part A				Part B[a]	Part C	
	Single intravenous dose				Multiple intravenous doses		
	Placebo[b]	Donanemab					
		10 mg/kg	20 mg/kg	40 mg/kg	10 mg/kg Q2W	10 mg/kg Q4W	20 mg/kg Q4W
Japanese	5 subjects	2 subjects	1 subject	2 subjects	3 subjects	3 subjects	2 subjects
Non-Japanese	10 subjects	5 subjects	6 subjects	2 subjects	7 subjects	5 subjects	8 subjects

[a] No subjects were randomized to donanemab 20 mg/kg.
[b] Pooled data from Parts A, B, and C

Table 22 shows the change from baseline in amyloid PET standardized uptake value ratio (SUVr) through Week 72, the primary endpoint for PD.

Table 22. Change from baseline in amyloid PET SUVr through Week 72 (FAS)

	Part A				Part B[a]	Part C	
	Single intravenous dose				Multiple intravenous doses		
	Placebo[b]	Donanemab					
		10 mg/kg	20 mg/kg	40 mg/kg	10 mg/kg Q2W	10 mg/kg Q4W	20 mg/kg Q4W
Baseline[c]	1.54 ± 0.18 (N = 15)	1.52 ± 0.21 (N = 7)	1.51 ± 0.15 (N = 7)	1.48 ± 0.22 (N = 4)	1.56 ± 0.11 (N = 10)	1.53 ± 0.27 (N = 8)	1.58 ± 0.17 (N = 10)
Week 12[c]	1.52 ± 0.17 (N = 14)	1.46 ± 0.20 (N = 7)	1.30 ± 0.19 (N = 7)	1.23 ± 0.19 (N = 4)	1.32 ± 0.13 (N = 10)	1.31 ± 0.14 (N = 8)	1.29 ± 0.20 (N = 10)
Change from baseline[d]	−0.024 ± 0.03	−0.074 ± 0.05	−0.225 ± 0.05	−0.283 ± 0.06	−0.239 ± 0.04	−0.232 ± 0.04	−0.275 ± 0.04
Week 24[c]	1.52 ± 0.14 (N = 13)	1.44 ± 0.25 (N = 7)	1.31 ± 0.19 (N = 7)	1.24 ± 0.20 (N = 4)	1.25 ± 0.16 (N = 10)	1.27 ± 0.12 (N = 8)	1.25 ± 0.29 (N = 10)
Change from baseline[d]	−0.015 ± 0.04	−0.090 ± 0.06	−0.218 ± 0.06	−0.271 ± 0.08	−0.305 ± 0.05	−0.274 ± 0.06	−0.319 ± 0.05
Week 36[c]	1.48 ± 0.19 (N = 10)	1.37 ± 0.14 (N = 6)	1.31 ± 0.16 (N = 7)	1.30 (N = 1)	1.22 ± 0.13 (N = 9)	1.20 ± 0.10 (N = 7)	1.15 ± 0.30 (N = 7)
Change from baseline[d]	−0.010 ± 0.04	−0.087 ± 0.06	−0.213 ± 0.06	−0.309 ± 0.11	−0.363 ± 0.05	−0.339 ± 0.06	−0.389 ± 0.05
Week 48[c]	1.48 ± 0.14 (N = 11)	1.46 ± 0.25 (N = 7)	1.34 ± 0.18 (N = 7)	1.31 (N = 1)	1.26 ± 0.15 (N = 9)	1.18 ± 0.08 (N = 6)	1.15 ± 0.32 (N = 5)
Change from baseline[d]	−0.037 ± 0.04	−0.074 ± 0.06	−0.181 ± 0.06	−0.268 ± 0.10	−0.323 ± 0.05	−0.329 ± 0.06	−0.390 ± 0.06
Week 72[c]	1.46 ± 0.16 (N = 11)	1.34 ± 0.14 (N = 6)	1.35 ± 0.21 (N = 6)	1.33 (N = 1)	1.28 ± 0.14 (N = 9)	1.12 ± 0.05 (N = 4)	1.00 ± 0.06 (N = 4)
Change from baseline[d]	−0.050 ± 0.04	−0.122 ± 0.06	−0.183 ± 0.06	−0.255 ± 0.10	−0.305 ± 0.05	−0.419 ± 0.06	−0.379 ± 0.05

[a] No subjects were randomized to donanemab 20 mg/kg.
[b] Pooled data from Parts A, B, and C
[c] Mean ± standard deviation
[d] Least squares mean ± standard error (analyzed with a mixed model for repeated measures [MMRM] with treatment, visit, treatment-by-visit interaction, baseline amyloid PET SUVr, and ApoE ε4 carrier status as fixed effects [an unstructured variance-covariance matrix was used for within-subject effects])

Table 23 shows the incidence of adverse events in subjects receiving a single dose.

Table 23. Incidence of adverse events (safety analysis set)

	Part A							
	Single intravenous dose							
	Placebo		Donanemab					
			10 mg/kg		20 mg/kg		40 mg/kg	
	Japanese (N = 2)	Non-Japanese (N = 5)	Japanese (N = 2)	Non-Japanese (N = 5)	Japanese (N = 1)	Non-Japanese (N = 6)	Japanese (N = 2)	Non-Japanese (N = 2)
Adverse events	50.0 (1)	80.0 (4)	100 (2)	100 (5)	0 (0)	100 (6)	100 (2)	100 (2)
Common events[a]								
Vasogenic cerebral oedema	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	33.3 (2)	100 (2)	0 (0)
Headache	0 (0)	0 (0)	0 (0)	20.0 (1)	0 (0)	33.3 (2)	0 (0)	0 (0)
Upper respiratory tract infection	0 (0)	40.0 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

% (n)

[a] Adverse events occurring in ≥2 subjects in either the placebo group or the donanemab group

	Part B[a]				Part C					
	Multiple intravenous doses									
	Placebo		Donanemab 10 mg/kg Q2W		Placebo		Donanemab			
							10 mg/kg Q4W		20 mg/kg Q4W	
	Japanese (N = 1)	Non-Japanese (N = 2)	Japanese (N = 3)	Non-Japanese (N = 7)	Japanese (N = 2)	Non-Japanese (N = 3)	Japanese (N = 3)	Non-Japanese (N = 5)	Japanese (N = 2)	Non-Japanese (N = 8)
Adverse events	0 (0)	100 (0)	100 (3)	100 (7)	50.0 (1)	100 (3)	100 (3)	100 (5)	50.0 (1)	100 (8)
Common events[b]										
Vasogenic cerebral oedema	0 (0)	0 (0)	33.3 (1)	14.3 (1)	0 (0)	0 (0)	33.3 (1)	40.0 (2)	0 (0)	37.5 (3)
Cerebral microhaemorrhage	0 (0)	0 (0)	33.3 (1)	14.3 (1)	50.0 (1)	0 (0)	0 (0)	0 (0)	0 (0)	25.0 (2)
Upper respiratory tract infection	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	33.3 (1)	0 (0)	40.0 (2)	0 (0)	12.5 (1)
Anger	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	66.7 (2)	0 (0)	0 (0)	0 (0)
Fatigue	0 (0)	0 (0)	0 (0)	28.6 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Rash	0 (0)	100 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

% (n)

[a] No subjects were randomized to donanemab 20 mg/kg.

[b] Adverse events occurring in ≥2 subjects in either the placebo group or the donanemab group

One subject in the placebo group died (myocardial infarction), but the death was considered unrelated to the study drug. Other serious adverse events occurred in 2 subjects in the placebo group (hip fracture and invasive lobular breast carcinoma), 1 subject in the donanemab 10 mg/kg group in Part C (anger), 2 subjects in the donanemab 20 mg/kg group in Part C (vasogenic cerebral oedema and urinary tract infection/decreased activity). Vasogenic cerebral oedema was considered related to the study drug. Adverse events led to study treatment discontinuation in 1 subject in the placebo group (myocardial infarction) and 2 subjects in the donanemab 20 mg/kg group in Part C (vasogenic cerebral oedema and hypertensive crisis).

7.3 Foreign phase II study (Study AACG, CTD 5.3.5.1.1 [December 2017 to December 2020])

A randomized, double-blind, placebo-controlled study was conducted at 56 study centers in foreign countries to investigate the efficacy and safety of donanemab in patients with early AD with low or medium tau levels

in the brain (target sample size, approximately 250 subjects [approximately 125 subjects each for the placebo and donanemab groups][12])

Study AACG consisted of a screening period (up to 9 weeks), a 72-week double-blind period, and a 48-week immunogenicity and safety follow-up period. Subjects were randomly assigned in a 1:1 ratio to placebo or donanemab,[13] and randomization was stratified by study center. During the double-blind period, subjects were to receive placebo or donanemab 1400 mg (700 mg for the first 3 doses) intravenously every 4 weeks. When the decrease in amyloid plaque as measured by amyloid PET scan with florbetapir (^{18}F) at Weeks 24 or 52 met the criteria, the dose level was reduced to donanemab 700 mg or changed to placebo under blinded conditions.[14] Subjects who completed Study AACG had the option to enter Study AACH, the open-label extension study.

Key eligibility criteria

Patients with early AD aged ≥60 years and ≤85 years who met the following conditions:

- Gradual and progressive change in memory function reported by the subject or study partner[15] for ≥6 months
- A positive[16] amyloid PET using florbetapir ^{18}F
- An MMSE score ≥20 and ≤28 at screening
- A tau level on flortaucipir (^{18}F) PET defined by SUVr from 1.10 to 1.46; or classified as progressive AD based on the accumulation pattern for tau deposits in the brain, with an SUVr of <1.10
- The MRI scans at screening did not show the following findings:
  - Amyloid related imaging abnormalities-edema/effusion (ARIA-E)
  - Five or more cerebral microhemorrhages
  - Two or more areas of superficial siderosis
  - Cerebral hemorrhage >1 cm
  - Severe white matter disease

12) The sample size was calculated assuming that the mean changes from baseline in iADRS at Month 18 in the placebo and the donanemab groups were −12 and −6, respectively, with a common standard deviation of 17. If approximately 200 subjects (100 subjects per treatment group) complete the double-blind period, this study design will provide approximately 84% power to demonstrate that the donanemab group has a ≥60% posterior probability of showing at least 3points decrease (25% decrease) in iADRS over placebo. With the sample size being the same as above, if there is no difference in iADRS decline between the groups, the posterior probability of achieving ≥60% is approximately 6% power.

13) Under Protocol Amendment (c) or earlier, subjects were randomly assigned in a 1:1:1 ratio to placebo, donanemab monotherapy, or donanemab in combination with oral β secretase inhibitor. Assignment to the donanemab combination therapy group was discontinued under Protocol amendment (d) (October 9, 2018). Subjects in the donanemab combination therapy group were allowed to continue the study by staying blinded and receiving donanemab intravenously every 4 weeks without oral β secretase inhibitor. However, data from these subjects were not to be used for the comparison of efficacy and safety between the donanemab and placebo groups.

14) Subjects whose amyloid plaque level was <11 Centiloids on a single PET scan were to switch to placebo, and subjects whose amyloid plaque level was ≥11 and <25 Centiloids on 2 consecutive PET scans were to have their dose reduced to donanemab 700 mg.

15) A person who was able to provide written informed consent for the patient's participation in the study, be in contact with the patient for at least 10 hours per week, and accompany the patient for study visits or be available by phone at designated times.

16) The patient was determined to be positive for amyloid plaques when the scan data met the central read criteria.

Patients taking symptomatic AD medication (cholinesterase [ChE] inhibitor and/or memantine) were allowed to participate in the study only if the dose level had remained unchanged for ≥2 months prior to baseline.[17)]

In the event of ARIA-E or ARIA-H, the recommendations shown below were to be followed (Table 24), and follow-up MRI scans, which were originally unscheduled, were to be performed every 4 to 6 weeks until resolution or stabilization of all ARIA-E and new ARIA-H.

Table 24. Actions taken in the event of ARIA-E or ARIA-H

Findings	Action
• Asymptomatic and mild ARIA-E on MRI	Continue treatment[a]
• Asymptomatic and moderate ARIA-E on MRI • Mild symptomatic and mild ARIA-E on MRI	Reduce dose from 1400 mg to 700 mg; or switch dose from 700 mg to placebo[a]
• ARIA-E other than those described above or below	Interrupt treatment
• A second occurrence of ARIA-E in patients who had previously had their dose reduced or interrupted • An increase in ARIA-H accompanied by clinical symptoms • Five or more new cerebral microhemorrhages • Two or more areas of new superficial siderosis • Worsening of superficial siderosis that had existed before the start of study drug • Cerebral hemorrhage regardless of symptoms • ARIA-E reported as a serious adverse event, regardless of symptoms or severity on MRI	Discontinue treatment

[a] The investigator was allowed to interrupt treatment after consultation with the sponsor.

All 257 randomized subjects (126 subjects and 131 subjects in the placebo and donanemab groups, respectively; the same applies hereinafter) were defined as the randomized population. Of these, 256 subjects who received at least 1 dose of study drug (125 subjects and 131 subjects) were included in the safety analysis set. Of the safety analysis set, 225 subjects (120 subjects and 125 subjects), who had iADRS results at baseline and at least 1 timepoint after baseline, were included in the FAS, which was the population for the primary efficacy analysis. A total of 69 subjects (32 subjects and 37 subjects) discontinued from the study with common reasons for discontinuation being “adverse events” in 26 subjects (6 subjects and 20 subjects) and “subject’s withdrawal” in 24 subjects (12 subjects and 12 subjects). In the donanemab group, at Week 72, 25% (19 of 77) of subjects were receiving 1400 mg, 23% (18 of 77) of subjects were receiving 700 mg, and 52% (40 of 77) of subjects were receiving 0 mg (placebo). Concomitant AD medications[18)] usedduring the study period were donepezil (130 subjects [62 subjects and 68 subjects]), rivastigmine (19 subjects [13 subjects and 6 subjects]), galantamine (15 subjects [6 subjects and 9 subjects]), and memantine (70 subjects [33 subjects and 37 subjects]). Table 25 shows the ApoE ε4 carrier status.

[17)] When initiating, discontinuing, or changing the dose of concomitant AD medication before the completion of the double-blind period, the sponsor or a designee had to determine, in advance, whether to continue the study or perform clinical evaluation.
[18)] ChE inhibitor and/or memantine

Table 25. ApoE ε4 carrier status in each group (randomized population)

ApoE ε4 carrier status	Placebo[a] (N = 124)	Donanemab (N = 131)
Carrier	74.2 (92)	72.5 (95)
Homozygous	22.6 (28)	19.1 (25)
Heterozygous	51.6 (64)	53.4 (70)
Non-carrier	25.8 (32)	27.5 (36)

% (n)
[a] Missing data for 2 subjects

Table 26 shows the change from baseline in iADRS[19] at Week 76, the primary endpoint. The difference between the placebo and donanemab groups was statistically significant.

Table 26. Change from baseline in iADRS at Week 76 (FAS)

	Placebo	Donanemab[a]
Baseline[b]	106.06 ± 13.050 (N = 120)	106.28 ± 12.728 (N = 125)
Week 76[b]	96.69 ± 18.593 (N = 91)	99.29 ± 17.494 (N = 93)
Change from baseline (MMRM)[c, d]	−10.07 ± 1.143	−6.84 ± 1.136
Between-group difference [two-sided 95% CI]	—	3.23 [0.15, 6.31]
P-value for between-group comparison[c, e]	—	0.040

[a] Data from the donanemab combination therapy group are not included.
[b] Mean ± standard deviation
[c] An MMRM with treatment, visit, treatment-by-visit interaction, pooled site, baseline AD medication (ChE inhibitor and/or memantine) use, baseline value, baseline age, and baseline value-by-visit interaction as fixed effects. An unstructured variance-covariance matrix was used for within-subject effects.
[d] Least squares mean ± standard error
[e] Significance level 0.05 (two-sided)

The secondary endpoints are tabulated below. Table 27 shows the changes from baseline at Week 76 in CDR-SB, Alzheimer's Disease Assessment Scale-13-item Cognitive subscale (ADAS-Cog13), Alzheimer's Disease Cooperative Study-Activities of Daily Living Inventory, instrumental items (ADCS-iADL), and MMSE; and Table 28 presents the change from baseline at Week 76 in brain Aβ plaques as measured by amyloid PET in Centiloids.

[19] iADRS score = [−1 (ADAS-Cog$_{13}$) + 85] + ADCS-iADL (*J Prev Alzheimers Dis.* 2015;2:227-41). If ADAS-Cog13 or ADCS-iADL is missing, iADRS will be regarded as missing data.

Table 27. Change from baseline at Week 76 in CDR-SB, ADAS-Cog13, ADCS-iADL, and MMSE (FAS)

		Placebo	Donanemab[a]
CDR-SB[e]	Baseline[b]	3.37 ± 1.703 (N = 120)	3.55 ± 2.043 (N = 125)
	Week 76[b]	4.89 ± 2.563 (N = 90)	4.84 ± 2.559 (N = 93)
	Change from baseline (MMRM)[c, d]	1.58 ± 0.178	1.22 ± 0.176
	Between-group difference [two-sided 95% CI]	—	−0.36 [−0.83, 0.12]
ADAS-Cog13[e]	Baseline[b]	27.53 ± 7.553 (N = 120)	27.68 ± 7.704 (N = 125)
	Week 76[b]	32.43 ± 9.606 (N = 93)	30.54 ± 10.022 (N = 93)
	Change from baseline (MMRM)[c, d]	4.77 ± 0.660	2.91 ± 0.659
	Between-group difference [two-sided 95% CI]	—	−1.86 [−3.63, −0.09]
ADCS-iADL[e]	Baseline[b]	48.58 ± 7.416 (N = 120)	48.96 ± 7.224 (N = 125)
	Week 76[b]	44.22 ± 10.851 (N = 91)	44.83 ± 10.343 (N = 93)
	Change from baseline (MMRM)[c, d]	−5.20 ± 0.743	−3.95 ± 0.738
	Between-group difference [two-sided 95% CI]	—	1.24 [−0.75, 3.24]
MMSE[e]	Baseline[b]	23.77 ± 2.878 (N = 115)	23.56 ± 3.033 (N = 121)
	Week 76[b]	20.59 ± 4.790 (N = 90)	21.14 ± 4.706 (N = 91)
	Change from baseline (MMRM)[c, d]	−2.98 ± 0.390	−2.35 ± 0.386
	Between-group difference [two-sided 95% CI]	—	0.64 [−0.40, 1.67]

[a] Data from the donanemab combination therapy group are not included.
[b] Mean ± standard deviation
[c] An MMRM with treatment, visit, treatment-by- visit interaction, pooled site, baseline AD medication (ChE inhibitor and/or memantine) use, baseline value, baseline age, and baseline value-by-visit interaction as fixed effects. An unstructured variance-covariance matrix was used for within-subject effects.
[d] Least squares mean ± standard error
[e] If any items consisting of CDR-SB, ADAS-Cog13, ADCS-iADL, or MMSE are missing, data are to be handled as follows: For CDR-SB, if one of 6 items are missing, the sum of the items are to be imputed by prorating the sum of the other 5 items so that the imputed score would not be greater than the maximum total score for CDR-SB. If ≥2 items are missing, the CDR-SB total score at that visit is regarded as missing. For ADAS-Cog13, if ≤4 of 13 items are missing, the total score is imputed by weighting each score of the non-missing items so that the maximum possible total score of the non-missing items would be 85. If ≥5 items are missing, the ADAS-Cog13 total score at that visit is regarded as missing. For ADCS-iADL, if <30% of items are missing, the total score is imputed by weighting each score of the non-missing items so that the imputed score would not be greater than the maximum total score for ADCS-iADL, in a manner similar to the procedure described above. If >30% of items are missing, the ADCS-iADL total score at that visit is regarded as missing. For MMSE, if any item is missing, data for MMSE at that visit are regarded as missing.

Table 28. Change from baseline at Week 76 in brain Aβ plaques as measured by amyloid PET in Centiloids (FAS)

	Placebo	Donanemab[a]
Baseline[b]	103.09 ± 33.841 (N = 112)	107.18 ± 33.938 (N = 121)
Week 76[b]	103.86 ± 35.046 (N = 91)	21.27 ± 28.769 (N = 90)
Change from baseline (MMRM)[c, d]	0.93 ± 2.739	−84.13 ± 2.723
Between-group difference [two-sided 95% CI]	—	−85.06 [−92.68, −77.43]

[a] Data from the donanemab combination therapy group are excluded.
[b] Mean ± standard deviation
[c] An MMRM with treatment, visit, treatment-by-visit interaction, baseline value, and baseline age as fixed effects. An unstructured variance-covariance matrix was used for within-subject effects.
[d] Least squares mean ± standard error

Table 29 shows the incidence of adverse events.

Table 29. Incidence of adverse events (safety analysis set)

	Placebo (N = 125)	Donanemab (N = 131)
Any adverse event	90.4 (113)	90.8 (119)
Common events[a]		
Amyloid related imaging abnormality-oedema/effusion	0.8 (1)	26.7 (35)
Superficial siderosis of central nervous system	3.2 (4)	13.7 (18)
Fall	15.2 (19)	13.0 (17)
Nausea	3.2 (4)	10.7 (14)
Urinary tract infection	4.0 (5)	9.9 (13)
Dizziness	12.0 (15)	8.4 (11)
Diarrhoea	4.0 (5)	8.4 (11)
Amyloid related imaging abnormality-microhaemorrhages and haemosiderin deposits	3.2 (4)	8.4 (11)
Headache	12.0 (15)	7.6 (10)
Arthralgia	8.0 (10)	7.6 (10)
Cerebral microhaemorrhage	2.4 (3)	7.6 (10)
Infusion related reaction	0 (0)	7.6 (10)
Upper respiratory tract infection	7.2 (9)	6.9 (9)
Pneumonia	4.0 (5)	5.3 (7)
Vomiting	2.4 (3)	5.3 (7)
Anxiety	1.6 (2)	5.3 (7)
Depression	6.4 (8)	4.6 (6)

% (n)

[a] Adverse events occurring in ≥5% of subjects in either group

In the placebo group, 1.6% (2 of 125) of subjects in the placebo group died (pneumonia aspiration in 1 subject and cardiac arrest in 1 subject) and 0.8% (1 of 131) of subjects in the donanemab group died (pneumonia). A causal relationship to the study drug was ruled out for all events. The incidence of serious adverse events was 17.6% (22 of 125 subjects) in the placebo group and 17.6% (23 of 131 subjects) in the donanemab group. Serious adverse events occurring in ≥1% in either group were pneumonia (0.8% and 3.8% in the placebo and the donanemab groups, respectively; the same applies hereinafter), dehydration (0.8% and 1.5%), hip fracture (1.6% and 0.8%), amyloid related imaging abnormality-oedema/effusion (0% and 1.5%), infusion related reaction (0% and 1.5%), pulmonary embolism (0% and 1.5%), and syncope (0% and 1.5%). Among these, all the events of amyloid related imaging abnormality-oedema/effusion and infusion related reaction, and 1 event of pneumonia (1 e subject) in the donanemab group were considered related to the study drug.

Adverse events led to study treatment discontinuation in 9 of 125 subjects (7.2%) in the placebo group and in 40 of 131 subjects (30.5%) in the donanemab group. Among these events, those occurring in ≥1% of subjects in either group were superficial siderosis of central nervous system (0.8% and 6.1%), amyloid related imaging abnormality-oedema/effusion (0.8% and 5.3%), infusion related reaction (0% and 5.3%), amyloid related imaging abnormality-microhaemorrhages and haemosiderin deposits (0% and 2.3%), and cerebral microhaemorrhage (0% and 1.5%). All these events were considered related to the study drug.

7.4 Global phase III study (Study AACI, CTD 5.3.5.1.2 [ongoing since June 2020, data cut-off in April 2023])

A randomized, double-blind, placebo-controlled study was conducted at 277 study centers in and outside Japan to verify the superior efficacy of donanemab over placebo in Japanese and non-Japanese patients with early

AD with low to high tau levels in the brain (target sample size, approximately 1,800 subjects [900 subjects each for placebo and donanemab groups][20]).

Table 30 shows the summary of main changes to the protocol of Study AACI.

Table 30. Summary of main changes to the protocol of Study AACI

Protocol	Main changes
Protocol version (a) (December 14, 2020)	When the study was initiated, subjects received placebo or donanemab 1400 mg intravenously every 4 weeks. At an early stage of the treatment (by Dose 3), serious ARIA-E was reported in 2 subjects. Therefore, the protocol was amended to modify the study design. Under Protocol version (a) and subsequent versions, donanemab at 700 mg was administered for the first 3 doses.
Protocol version (b) (February 17, 2021)	➢ Positioning of study: The study was designed as a phase II study at the start of the study; however, the study was changed to a confirmatory study (phase III) to confirm the reproducibility of the results obtained in Study AACG. ➢ Primary endpoint: CDR-SB was used as the primary endpoint from the original protocol at the start of study to Protocol version (a); however, it was changed to iADRS to confirm the reproducibility of the results obtained in Study AACG. ➢ Primary analysis model: The analysis method was changed from MMRM to a Bayesian Disease Progression Model (DPM) because of the change of the primary endpoint or other reasons. ➢ Primary analysis populations: The "overall population or low-medium tau population as assessed by PET" was primary analysis population at the start of the study. However, based on the results of Study AACG, it was changed to the "low-medium tau population as assessed by PET." ➢ Target sample size: An overall population of approximately 500 subjects was increased to a low-medium tau population of approximately 1,000 subjects (an overall population of approximately 1,500 subjects) because of the changes in the primary endpoint or other reasons.
Addendum 9 ([redacted], 20[redacted])	An unblinded safety evaluation group was added to obtain the safety information required for the submission of Biologics License Application (BLA) in the US.
Protocol version (c) (September 3, 2021)	To submit part of data from the double-blind group as safety data for BLA in the US, 300 subjects were additionally enrolled in the double-blind period to include a total of 1,800 subjects.
Protocol version (d) (October 5, 2021)	➢ Study period: A long-term extension period was added to accrue data on the safety and efficacy of donanemab. ➢ Primary analysis population: The primary analysis population was changed again to "overall population or low-medium tau population as assessed by PET." ➢ Safety evaluation: An additional step is added to the procedure to allow the detection of ARIA and its severity at an earlier stage. In the revised procedure, MRI at Week 4 enables the assessment of the results before the second dose of the study drug.
Protocol version (e) (November 10, 2022)	➢ Primary analysis model: The analysis method was changed from DPM to a natural cubic spline (NCS) model with 2 degrees of freedom.

Study AACI consisted of a lead-in period (anytime prior to complete screening), a complete screening period (up to 7 weeks), a double-blind period (76 weeks), an extension period (78 weeks), and a follow-up period (up to 44 weeks). Subjects were randomly assigned in a 1:1 ratio to receive placebo or donanemab, with study center and brain tau category (low-medium versus high) as stratification factors. In the double-blind period, subjects were to receive placebo or donanemab 1400 mg (700 mg for the first 3 doses[21]) intravenously every 4 weeks. In the extension period, all subjects who had been on placebo in the double-blind period were assigned to receive donanemab. Subjects randomized to donanemab during the double-blind period who met the dose cessation criteria based on amyloid plaque reduction measured by amyloid PET scan by Week 76 were assigned

[20] The target sample size for the low-medium tau pathology population specified in Protocol version (c) was determined as follows: Assumptions were based on the results from Study AACG. Assuming that the mean change form baseline in iADRS at Month 18 in the placebo and donanemab groups was −10.06 and −6.86, respectively, with a common standard deviation of 11.06, with assumed drop-out rate of 30%, it was determined that a sample size of approximately 1,000 subjects would provide >95% statistical power to achieve a statistical significance level of 0.05 (two-sided) for statistically significant difference between the placebo and donanemab groups using the natural cubic spline model with 2 degrees of freedom (NCS2).

[21] Subjects who had developed ARIA during the first 3 doses were allowed to remain on 700 mg thereafter at the principal investigator's or investigator's discretion.

to receive placebo. Subjects randomized to donanemab during the double-blind period who did not meet the dose cessation criteria were assigned to receive donanemab. The extension period was double-blinded. During the extension period, subjects received donanemab 1400 mg (700 mg for the first 3 doses for subjects who had been on placebo during the double-blind period) intravenously every 4 weeks. Subjects who had remained on donanemab 700 mg during the double-blind period were allowed to have their dose escalated to 1400 mg at Visit 25 or later. Subjects who met the dose cessation criteria [22)] based on a reduction in amyloid plaque measured by amyloid PET using florbetapir (^{18}F) or florbetaben (^{18}F) at Weeks 24, 52, 76, 102, and 130 were assigned to receive placebo in a double-blinded manner (Figure 1). This section describes the results up to the end of the double-blind period submitted at the filing of the present application.

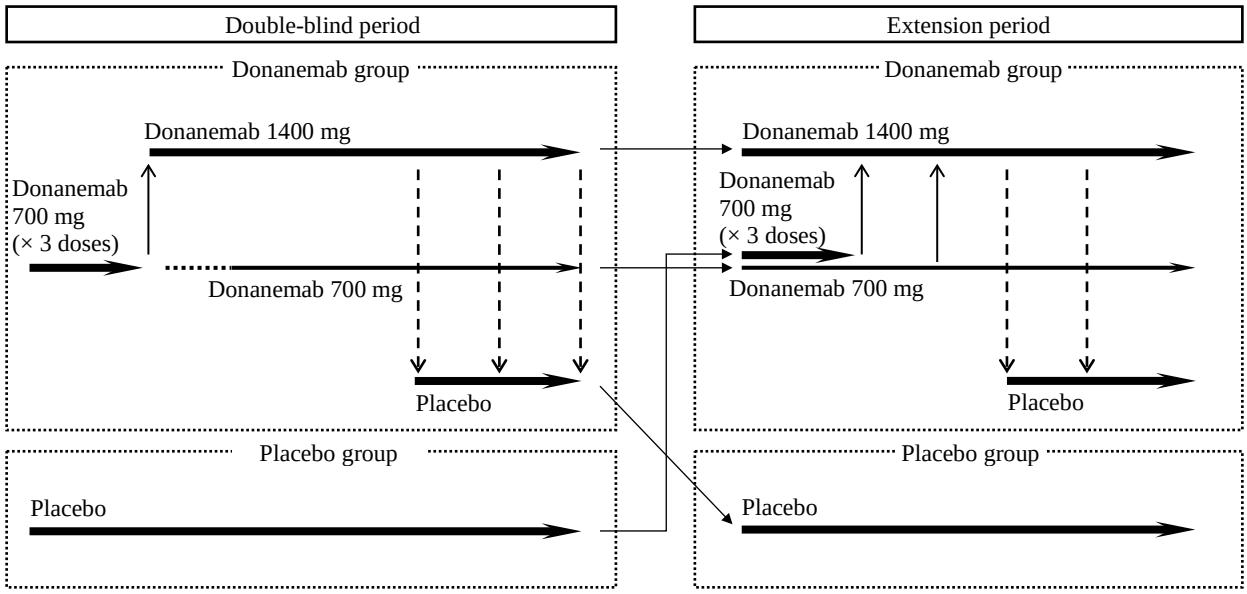


Figure 1. Outline of AACI study design

Key eligibility criteria

Patients with early AD aged ≥60 years and ≤85 years who met the following conditions:

- Gradual and progressive change in memory function reported by the subject or study partner[15)] for ≥6 months
- A positive[16)] amyloid PET using florbetapir (^{18}F) or florbetaben (^{18}F)[23)]
- An MMSE score of ≥20 and ≤28 in the lead-in period or at screening
- The results of tau PET using flortaucipir (^{18}F) met the criteria[24)]
- The MRI scans at screening did not show the following:
  - ARIA-E
  - Five or more cerebral microhemorrhages
  - More than 1 area of superficial siderosis

22) Amyloid level <11 Centiloids on a single PET scan or ≥11 and <25 Centiloids on 2 consecutive PET scans.
23) Only florbetapir (^{18}F) was used in Japan.
24) Low-medium brain tau level: Corresponds to AD with intermediate brain tau burden by visual read (*JAMA Neurol.* 2020;77:829-39), with an SUVr ≥1.10 and ≤1.46; or corresponds to AD with high brain tau burden by visual read, with an SUVr ≤1.46
High brain tau level: Corresponds to AD with intermediate or high brain tau burden by visual read, with SUVr >1.46

- Cerebral hemorrhage
- Severe white matter disease

Patients taking symptomatic AD medications (ChE inhibitor and/or memantine) were allowed to participate in the study only if the dose level had remained unchanged for ≥30 days prior to baseline. However, the initiation, increase, or discontinuation of these medications was permitted if considered medically necessary.

In the event of ARIA-E or ARIA-H, the principal investigator had to decide to discontinue or resume the study drug according to the instruction below, using the guidance presented in the operation manual as reference (Table 31). To make a decision to discontinue or resume the study drug, the principal investigator could discuss this matter with the sponsor-designated medical expert.

- The principal investigator should interrupt the study drug if the ARIA-E or ARIA-H is deemed to be clinically relevant by the principal investigator.
- In the event of a new ARIA-E or ARIA-H, the principal investigator should discontinue or interrupt the study drug according to the MRI findings and the severity of symptoms to monitor the patient's symptoms and perform MRI scans every 4 to 6 weeks. After resolution of ARIA-E or stabilization of ARIA-H is confirmed, treatment may be resumed.

Table 31. Guidance in the operation manual for Study AACI

Findings	Asymptomatic/symptomatic	Severity on MRI[a]	Guidance
ARIA-E	Asymptomatic	Mild, mild+, moderate	• In the event of moderate ARIA-E occurring during the first 3 doses, interrupt study treatment. For other cases, study treatment may be continued.
		Moderate+, severe	• Interrupt study treatment. • If ARIA-E resolved on MRI, consider resuming study treatment. • If ARIA-E do not resolve on MRI, permanently discontinue study treatment.
	Symptomatic	Any degree of severity	• Interrupt study treatment. • If ARIA-E and clinical symptoms resolved, consider resuming study treatment. • If ARIA-E or clinical symptoms do not resolve, permanently discontinue study treatment. • If symptoms of ARIA-E are clearly related to SAE, permanently discontinue study treatment.
ARIA-H (cerebral microhemorrhage, superficial siderosis)	Asymptomatic	After baseline, ≤10 new cerebral microhemorrhages and/or ≤2 new areas of superficial siderosis	• During the first 3 doses of study drug, if >4 new cerebral microhemorrhages or ≥1 area of superficial siderosis occur, interrupt study treatment. For other cases, study treatment may be continued.
		After baseline, >10 new cerebral microhemorrhages and/or >2 new areas of superficial siderosis	• Interrupt study treatment. • If an MRI shows stabilized cerebral microhemorrhage, consider resuming study treatment.
	Symptomatic	Any degree of severity	• Interrupt study treatment. • If symptoms do not resolve, permanently discontinue study treatment. • If symptoms for ARIA-H are clearly related to SAE, permanently discontinue study treatment.
ARIA-H (major hemorrhage [≥1 cm cerebral hemorrhage])	Asymptomatic/symptomatic	Any degree of severity	• Permanently discontinue study treatment.

[a] Detailed severity classification of ARIA-E on MRI is as follows:
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 <5 cm in single greatest dimension. Only 1 site of involvement is detected.
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 <5 cm in single greatest dimension. More than 1 site of involvement is detected.
Moderate = Moderate involvement (area of FLAIR hyperintensity measuring 5-10 cm in single greatest dimension). Only 1 site of involvement is detected.
Moderate+= Moderate involvement (area of FLAIR hyperintensity measuring 5-10 cm in single greatest dimension) in more than 1 site of involvement, each measuring <10 cm in single greatest dimension.
Severe = Severe involvement (area of FLAIR hyperintensity measuring >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.

Overall population

A total of 1,736 randomized subjects (876 subjects and 860 subjects in the placebo and donanemab groups, respectively; the same applies hereinafter) were included in the intent-to-treat (ITT) population. Of these, 1,727 subjects (874 subjects and 853 subjects) who received at least 1 dose of the study drug were included in the safety analysis set. The evaluable efficacy set (EES)[25)] was defined as the group of subjects with efficacy endpoint data at baseline and at ≥1 post-baseline time point. A total of 404 subjects (173 subjects and 231

[25)] The number of subjects included in the EES differs from one endpoint to another.

subjects) were discontinued from the study, with common reasons being "subject's withdrawal" in 205 subjects (94 subjects and 111 subjects) and "adverse events" in 71 subjects (21 subjects and 50 subjects). In the donanemab group, 69.2% (429 of 620) of subjects met the criteria for switching to placebo by Week 76. The symptomatic AD medications[26)] used concomitantly during the study period were donepezil (847 subjects [429 subjects and 418 subjects]), rivastigmine (150 subjects [77 subjects and 73 subjects]), galantamine (76 subjects [41 subjects and 35 subjects]), and memantine (439 subjects [231 subjects and 208 subjects]). Table 32 shows the ApoE ε4 carrier status.

Table 32. ApoE ε4 carrier status in each group (ITT)

ApoE ε4 carrier status	Placebo[a] (N = 872)	Donanemab[a] (N = 857)
Carrier	71.2 (621)	69.8 (598)
Homozygous	16.7 (146)	16.7 (143)
Heterozygous	54.5 (475)	53.1 (455)
Non-carrier	28.8 (251)	30.2 (259)

% (n)

[a] Missing data for 4 subjects in the placebo group and 3 subjects in the donanemab group

Table 33 shows the change from baseline in iADRS[19)] at Week 76, the primary efficacy endpoint. In both overall population (EES) and low-medium tau population (EES), both of which are populations for primary analysis, the results demonstrated the superiority of donanemab over placebo in slowing down iADRS progression.

Table 33. Change from baseline in iADRS at Week 76 (EES)

	Overall population		Low-medium tau population	
	Placebo	Donanemab	Placebo	Donanemab
Baseline[a]	103.82 ± 13.88 (N = 824)	104.55 ± 13.90 (N = 775)	105.95 ± 13.42 (N = 560)	105.92 ± 13.72 (N = 533)
Week 76[a]	93.82 ± 20.38 (N = 653)	96.98 ± 20.87 (N = 583)	98.88 ± 17.95 (N = 444)	101.31 ± 18.23 (N = 418)
Change from baseline (NCS2)[b, c]	−13.11 ± 0.50	−10.19 ± 0.53	−9.27 ± 0.49	−6.02 ± 0.50
Between-group difference [two-sided 95% CI][b]	—	2.92 [1.508, 4.331]	—	3.25 [1.883, 4.618]
P-value for between-group comparison[b, d]	—	<0.001	—	<0.001

[a] Mean ± standard deviation

[b] An NCS2 model with basis expansion terms (2 terms), NCS basis expansion term (2 terms)-by-treatment interaction, baseline age, pooled site, baseline brain tau category (low-medium or high), and baseline symptomatic AD medication (ChE inhibitor and/or memantine) use as fixed effects. In the analysis with the low-medium tau population, baseline brain tau category was removed from the model. An unstructured variance-covariance matrix was used for within-subject effects.

[c] Least squares mean ± standard error

[d] Taking into account the multiplicity arising from conducting an evaluation in 2 populations, a significance level of 0.01 (two-sided) for between-group comparison in the overall population, and a significance level of 0.04 (two-sided) for between-group comparison in the low-medium tau population were selected.

The secondary endpoints are tabulated below. Table 34 shows the changes from baseline at Week 76 in CDR-SB, ADAS-Cog13, ADCS-iADL, and MMSE, and Table 35 shows the change from baseline at Week 76 in brain Aβ plaques as measured by amyloid PET in Centiloids.

26) ChE inhibitor and/or memantine

Table 34. Change from baseline at Week 76 in CDR-SB, ADAS-Cog13, ADCS-iADL, and MMSE (EES)

		Overall population		Low-medium tau population	
		Placebo	Donanemab	Placebo	Donanemab
CDR-SB[e]	Baseline[a]	3.89 ± 2.034 (N = 838)	3.92 ± 2.055 (N = 794)	3.64 ± 1.986 (N = 569)	3.72 ± 2.088 (N = 546)
	Week 76[a]	5.80 ± 3.223 (N = 672)	5.25 ± 3.207 (N = 598)	5.13 ± 2.929 (N = 459)	4.64 ± 2.903 (N = 424)
	Change from baseline (MMRM)[b, c]	2.42 ± 0.092	1.72 ± 0.096	1.88 ± 0.102	1.20 ± 0.105
	Between-group difference [two-sided 95% CI]	—	−0.70 [−0.95, −0.45]	—	−0.67 [−0.95, −0.40]
ADAS-Cog13[e]	Baseline[a]	29.16 ± 8.85 (N = 841)	28.53 ± 8.78 (N = 797)	27.60 ± 8.21 (N = 570)	27.41 ± 8.44 (N = 550)
	Week 76[a]	34.53 ± 12.00 (N = 677)	32.72 ± 12.44 (N = 607)	31.17 ± 10.37 (N = 460)	29.77 ± 10.65 (N = 431)
	Change from baseline (NCS2)[d, c]	6.79 ± 0.27	5.46 ± 0.28	4.69 ± 0.26	3.17 ± 0.27
	Between-group difference [two-sided 95% CI]	—	−1.33 [−2.086, −0.565]	—	−1.52 [−2.250, −0.794]
ADCS-iADL[e]	Baseline[a]	47.98 ± 7.70 (N = 826)	47.96 ± 7.85 (N = 780)	48.56 ± 7.70 (N = 562)	48.20 ± 7.88 (N = 535)
	Week 76[a]	43.30 ± 10.61 (N = 661)	44.53 ± 11.06 (N = 591)	45.10 ± 9.82 (N = 451)	46.12 ± 10.26 (N = 420)
	Change from baseline (NCS2)[d, c]	−6.13 ± 0.30	−4.42 ± 0.32	−4.59 ± 0.32	−2.76 ± 0.34
	Between-group difference [two-sided 95% CI]	—	1.70 [0.840, 2.566]	—	1.83 [0.913, 2.748]
MMSE[e]	Baseline[a]	22.20 ± 3.90 (N = 841)	22.52 ± 3.84 (N = 796)	22.88 ± 3.74 (N = 573)	23.11 ± 3.64 (N = 549)
	Week 76[a]	19.79 ± 5.51 (N = 679)	20.71 ± 5.52 (N = 600)	21.30 ± 4.82 (N = 465)	22.00 ± 4.90 (N = 429)
	Change from baseline (NCS2)[d, c]	−2.94 ± 0.13	−2.47 ± 0.14	−2.09 ± 0.14	−1.61 ± 0.14
	Between-group difference [two-sided 95% CI]	—	0.47 [0.104, 0.841]	—	0.48 [0.089, 0.868]

[a] Mean ± standard deviation

[b] An MMRM with treatment, visit, treatment-by-visit interaction, baseline value, baseline value-by-visit interaction, baseline age, pooled site, baseline brain tau category (low-medium or high), and baseline symptomatic AD medication (ChE inhibitor and/or memantine) use as fixed effects. In the analysis with the low-medium tau population, baseline brain tau category was removed from the model. An unstructured variance-covariance matrix was used for within-subject effects.

[c] Least squares mean ± standard error

[d] An NCS2 model with basis expansion terms (2 terms), NCS basis expansion term (2 terms)-by-treatment interaction, baseline age, pooled site, baseline brain tau catogory (low-medium or high), and baseline symptomatic AD medication (ChE inhibitor and/or memantine) use as fixed effects. In the analysis with the low-medium tau population, baseline brain tau category was removed from the model. An unstructured variance-covariance matrix was used for within-subject effects.

[e] See Note e to Table 27.

Table 35. Change from baseline at Week 76 in brain Aβ plaques as measured by amyloid PET in Centiloids (EES)

	Overall population		Low-medium tau population	
	Placebo	Donanemab	Placebo	Donanemab
Baseline[a]	101.75 ± 34.371 (N = 812)	104.02 ± 34.417 (N = 765)	100.94 ± 35.264 (N = 556)	103.00 ± 34.800 (N = 525)
Week 76[a]	101.78 ± 35.710 (N = 690)	14.95 ± 22.820 (N = 614)	101.58 ± 36.548 (N = 470)	13.36 ± 22.375 (N = 433)
Change from baseline (MMRM)[b, c]	−0.67 ± 0.909	−87.03 ± 0.950	0.18 ± 1.065	−88.03 ± 1.104
Between-group difference [two-sided 95% CI]	—	−86.37 [−88.87, −83.87]	—	−88.21 [−91.22, −85.20]

[a] Mean ± standard deviation
[b] An MMRM with treatment, visit, treatment-by-visit interaction, baseline value, baseline value-by-visit interaction, baseline age, and baseline brain tau category (low-medium or high) as fixed effects. In the analysis with the low-medium tau population, baseline brain tau category was removed from the model. An unstructured variance-covariance matrix was used for within-subject effects.
[c] Least squares mean ± standard error

Table 36 shows the incidence of adverse events.

Table 36. Incidence of adverse events (safety analysis set)

	Placebo (N = 874)	Donanemab (N = 853)
Any adverse event	82.2 (718)	89.0 (759)
Common events[a]		
Amyloid related imaging abnormality-oedema/effusion	1.9 (17)	24.0 (205)
Amyloid related imaging abnormality-microhaemorrhages and haemosiderin deposits	7.4 (65)	19.7 (168)
COVID-19	17.6 (154)	15.9 (136)
Headache	9.8 (86)	14.0 (119)
Fall	12.6 (110)	13.4 (114)
Infusion related reaction	0.5 (4)	8.7 (74)
Superficial siderosis of central nervous system	1.1 (10)	6.8 (58)
Dizziness	5.5 (48)	6.2 (53)
Arthralgia	4.8 (42)	5.7 (49)
Urinary tract infection	6.8 (59)	5.3 (45)
Diarrhoea	5.7 (50)	5.0 (43)
Fatigue	5.1 (45)	4.9 (42)

% (n)
[a] Adverse events occurring in ≥5% of subjects in either group

Death occurred in 1.1% of subjects in the placebo group (10 of 874 subjects; pneumonia [2 subjects], myocardial infarction [1 subject], respiratory failure [1 subject], sepsis [1 subject], completed suicide/carbon monoxide poisoning [1 subject], death [1 subject], respiratory fume inhalation disorder [1 subject], dementia Alzheimer's type [1 subject], and arteriosclerosis [1 subject]) and in 1.9% of subjects in the donanemab group (16 of 853 subjects; death [3 subjects], pulmonary embolism [2 subjects], completed suicide [2 subjects], retroperitoneal haemorrhage [1 subject], COVID-19 [1 subject], subarachnoid haemorrhage [1 subject], dementia Alzheimer's type [1 subject], COVID-19 pneumonia [1 subject], respiratory arrest [1 subject], amyloid related imaging abnormality-microhaemorrhages and haemosiderin deposits [1 subject], dehydration [1 subject], and amyloid related imaging abnormality-oedema/effusion [1 subject]). Among these, the following events were considered related to the study drug: arteriosclerosis in the placebo group; and death (1 subject), amyloid related imaging abnormality-microhaemorrhages and haemosiderin deposits, and amyloid related imaging abnormality-oedema/effusion in the donanemab group. The incidence of serious adverse events

was 15.8% (138 of 874 subjects) in the placebo group and 17.4% (148 of 853 subjects) in the donanemab group. Serious adverse events occurring in ≥1% of subjects in either group were amyloid related imaging abnormality-oedema/effusion (0% and 1.5% in the placebo and the donanemab groups, respectively; the same applies hereinafter), syncope (1.5% and 1.1%), and COVID-19 (0.5% and 1.1%). Among these, all the events of amyloid related imaging abnormality-oedema/effusion and syncope (1 subject) in the donanemab group were considered related to the study drug.

Adverse events led to treatment discontinuation in 4.3% (38 of 874) of subjects in the placebo group and 13.1% (112 of 853) subjects in the donanemab group. Among these events, those occurring in ≥0.5% of subjects in either group were infusion related reaction (0% and 3.6%), amyloid related imaging abnormality-oedema/effusion (0.3% and 2.5%), amyloid related imaging abnormality-microhaemorrhages and haemosiderin deposits (0.2% and 0.8%), and hypersensitivity (0% and 0.5%). All the events were considered related to the study drug except for amyloid related imaging abnormality-microhaemorrhages and haemosiderin deposits (1 subject) in the donanemab group.

Japanese population

Of the 88 randomized Japanese patients who received the study drug (43 subjects and 45 subjects in the placebo and the donanemab groups, respectively; the same applies hereinafter), 14 subjects (7 subjects and 7 subjects) were discontinued from the study, with common reasons being “subject’s withdrawal” in 7 subjects (2 subjects and 5 subjects) and “adverse events” in 4 subjects (3 subjects and 1 subject). The symptomatic AD medications[27)] used concomitantly during the study period were donepezil (39 subjects [18 subjects and 21 subjects]), rivastigmine (6 subjects [4 subjects and 2 subjects]), galantamine (14 subjects [5 subjects and 9 subjects]), and memantine (2 subjects [1 subject and 1 subject]). Table 37 shows the ApoE ε4 carrier status.

Table 37. ApoE ε4 carrier status in each group (ITT, Japanese population)

ApoE ε4 carrier status	Placebo (N = 43)	Donanemab (N = 45)
Carrier	53.5 (23)	68.9 (31)
Homozygous	11.6 (5)	17.8 (8)
Heterozygous	41.9 (18)	51.1 (23)
Non-carrier	46.5 (20)	31.1 (14)

% (n)

Table 38 shows the change from baseline in iADRS at Week 76, the primary efficacy endpoint.

27) ChE inhibitor and/or memantine

Table 38. Change from baseline in iADRS at Week 76 (EES, Japanese population)

	Overall population		Low-medium tau population	
	Placebo	Donanemab	Placebo	Donanemab
Baseline[a]	100.52 ± 12.84 (N = 42)	103.09 ± 10.77 (N = 43)	102.17 ± 13.03 (N = 35)	102.47 ± 10.86 (N = 38)
Week 76[a]	90.94 ± 14.10 (N = 36)	98.80 ± 14.22 (N = 35)	93.27 ± 14.02 (N = 30)	98.75 ± 14.66 (N = 32)
Change from baseline (NCS2)[b, c]	−11.42 ± 1.62	−6.99 ± 1.62	−9.94 ± 1.78	−5.94 ± 1.71
Between-group difference [two-sided 95% CI]	—	4.43 [−0.173, 9.031]	—	3.99 [−0.978, 8.966]

[a] Mean ± standard deviation
[b] An NCS2 model with basis expansion terms (2 terms), NCS basis expansion term (2 terms)-by-treatment interaction, baseline age, pooled site, baseline brain tau category (low-medium or high), and baseline symptomatic AD medication (ChE inhibitor and/or memantine) use as fixed effects. In the analysis with the low-medium tau population, baseline brain tau category was removed from the model. An unstructured variance-covariance matrix was used for within-subject effects.
[c] Least squares mean ± standard error

The secondary endpoints are tabulated below. Table 39 shows the changes from baseline at Week 76 in CDR-SB, ADAS-Cog13, ADCS-iADL, and MMSE, and Table 40 shows the change from baseline at Week 76 in brain Aβ plaques as measured by amyloid PET in Centiloids.

Table 39. Change from baseline at Week 76 in CDR-SB, ADAS-Cog13, ADCS-iADL, and MMSE (EES, Japanese population)

		Overall population		Low-medium tau population	
		Placebo	Donanemab	Placebo	Donanemab
CDR-SB[e]	Baseline[a]	3.80 ± 2.223 (N = 42)	3.59 ± 1.695 (N = 43)	3.51 ± 2.215 (N = 35)	3.59 ± 1.720 (N = 38)
	Week 76[a]	5.49 ± 3.190 (N = 36)	4.76 ± 2.840 (N = 36)	4.78 ± 2.824 (N = 30)	4.52 ± 2.690 (N = 32)
	Change from baseline (MMRM)[b, c]	1.64 ± 0.422	1.40 ± 0.430	1.14 ± 0.407	1.23 ± 0.394
	Between-group difference [two-sided 95% CI]	—	−0.23 [−1.33, 0.87]	—	0.08 [−1.03, 1.20]
ADAS-Cog13[e]	Baseline[a]	29.98 ± 7.43 (N = 43)	29.75 ± 6.21 (N = 44)	29.03 ± 7.40 (N = 36)	29.85 ± 6.15 (N = 39)
	Week 76[a]	35.25 ± 8.77 (N = 36)	31.78 ± 6.92 (N = 36)	33.43 ± 8.45 (N = 30)	31.42 ± 6.95 (N = 33)
	Change from baseline (NCS2)[c, d]	5.40 ± 0.80	2.68 ± 0.80	3.90 ± 0.80	2.38 ± 0.76
	Between-group difference [two-sided 95% CI]	—	−2.71 [−4.969, −0.458]	—	−1.52 [−3.716, 0.673]
ADCS-iADL[e]	Baseline[a]	45.57 ± 7.90 (N = 42)	47.91 ± 6.76 (N = 43)	46.26 ± 7.36 (N = 35)	47.39 ± 6.93 (N = 38)
	Week 76[a]	41.19 ± 8.21 (N = 36)	45.14 ± 10.57 (N = 36)	41.70 ± 8.45 (N = 30)	45.16 ± 10.73 (N = 32)
	Change from baseline (NCS2)[c, d]	−4.60 ± 1.32	−3.37 ± 1.31	−4.67 ± 1.47	−3.12 ± 1.42
	Between-group difference [two-sided 95% CI]	—	1.24 [−2.442, 4.913]	—	1.54 [−2.545, 5.631]
MMSE[e]	Baseline[a]	22.60 ± 3.01 (N = 43)	22.86 ± 2.83 (N = 44)	22.92 ± 3.04 (N = 36)	22.90 ± 2.89 (N = 39)
	Week 76[a]	20.36 ± 3.79 (N = 36)	21.47 ± 3.05 (N = 36)	21.37 ± 3.17 (N = 30)	21.76 ± 2.93 (N = 33)
	Change from baseline (NCS2)[c, d]	−2.84 ± 0.45	−1.76 ± 0.45	−2.11 ± 0.48	−1.56 ± 0.46
	Between-group difference [two-sided 95% CI]	—	1.08 [−0.184, 2.350]	—	0.55 [−0.773, 1.872]

[a] Mean ± standard deviation

[b] An MMRM with treatment, visit, treatment-by-visit interaction, baseline value, baseline value-by-visit interaction, baseline age, pooled site, baseline brain tau category (low-medium or high), and baseline symptomatic AD medication (ChE inhibitor and/or memantine) use as fixed effects. In the analysis with the low-medium tau population, baseline brain tau category was removed from the model. An unstructured variance-covariance matrix was used for within-subject effects.

[c] Least squares mean ± standard error

[d] An NCS2 model with basis expansion terms (2 terms), NCS basis expansion term (2 terms)-by-treatment interaction, baseline age, pooled site, baseline brain tau category (low-medium or high), and baseline symptomatic AD medication (ChE inhibitor and/or memantine) use as fixed effects. In the analysis with the low-medium tau population, baseline brain tau category was removed from the model. An unstructured variance-covariance matrix was used for within-subject effects.

[e] See Note e to Table 27.

Table 40. Change from baseline at Week 76 in brain Aβ plaques as measured by amyloid PET in Centiloids (EES, Japanese population)

	Overall population		Low-medium tau population	
	Placebo	Donanemab	Placebo	Donanemab
Baseline[a]	85.14 ± 27.868 (N = 40)	82.76 ± 30.770 (N = 43)	87.31 ± 29.802 (N = 33)	82.33 ± 29.680 (N = 38)
Week 76[a]	91.68 ± 33.767 (N = 36)	9.49 ± 22.294 (N = 36)	93.31 ± 35.558 (N = 30)	7.70 ± 22.072 (N = 32)
Change from baseline (MMRM)[b, c]	6.49 ± 3.621	−72.27 ± 3.924	5.07 ± 3.506	−74.91 ± 3.364
Between-group difference [two-sided 95% CI]	—	−78.76 [−87.54, −69.98]	—	−79.98 [−89.76, −70.20]

[a] Mean ± standard deviation
[b] An MMRM with treatment, visit, treatment-by-visit interaction, baseline value, baseline value-by-visit interaction, baseline age, and baseline brain tau category (low-medium or high) as fixed effects. In the analysis with the low-medium tau population, baseline brain tau category was removed from the model. An unstructured variance-covariance matrix was used for within-subject effects.
[c] Least squares mean ± standard error

Table 41 shows the incidence of adverse events.

Table 41. Incidence of adverse events (safety analysis set, Japanese population)

	Placebo (N = 43)	Donanemab (N = 45)
Any adverse event	76.7 (33)	91.1 (41)
Common events[a]		
Amyloid related imaging abnormality-microhaemorrhages and haemosiderin deposits	7.0 (3)	26.7 (12)
Amyloid related imaging abnormality-oedema/effusion	2.3 (1)	22.2 (10)
COVID-19	4.7 (2)	13.3 (6)
Arthralgia	0 (0)	11.1 (5)
Nasopharyngitis	2.3 (1)	6.7 (3)
Back pain	2.3 (1)	6.7 (3)
Infusion related reaction	0 (0)	6.7 (3)
Contusion	7.0 (3)	4.4 (2)
Delirium	9.3 (4)	2.2 (1)
Tinea pedis	7.0 (3)	2.2 (1)

% (n)
[a] Adverse events occurring in ≥5% of subjects in either group

There were no deaths. The incidence of serious adverse events was 18.6% (8 of 43 subjects) in the placebo group and 15.6% (7 of 45 subjects) in the donanemab group. No serious adverse events occurred in ≥2 subjects in either group.

Adverse events led to treatment discontinuation in 7.0% of subjects in the placebo group (3 of 43 subjects; amyloid related imaging abnormality-oedema/effusion, electrocardiogram QT prolonged, and rectal cancer in 1 subject each) and 8.9% of subjects in the donanemab group (4 of 45 subjects; amyloid related imaging abnormality-oedema/effusion [2 subjects] and infusion related reaction [2 subjects]). All these events were considered related to the study drug.

7.5 Global phase III study (Study AACI Addendum 9, CTD 5.3.5.1.2 [ongoing since [redacted] 20[redacted], data cut-off in [redacted] 20[redacted]])

An open-label, uncontrolled study was conducted at 122 study centers in and outside Japan to evaluate the long-term safety of donanemab in Japanese and non-Japanese patients with early AD (target sample size, a maximum of approximately 1,000 subjects [90 Japanese subjects]).

Study AACI Addendum 9 consisted of a lead-in period (anytime prior to complete screening), a complete screening period (up to 7 weeks), an open-label period (72 weeks), and a follow-up period (up to 44 weeks). In the open-label period, subjects were to receive donanemab 1400 mg (700 mg for the first 3 doses) as an intravenous infusion every 4 weeks. Treatment with donanemab was to be discontinued in patients whose amyloid plaque reduction as measured by amyloid PET scan at Weeks 24 and 52 met the dose cessation criteria.[22)]

Key eligibility criteria were similar to those used in Study AACI but included no criteria for tau PET.

A total of 1,047 subjects (including 57 Japanese subjects) received the study drug and were included in the safety analysis set. Of the safety analysis set, as of the data-cut-off date, 900 subjects (86.0%) had received ≥6 doses, and 487 subjects (46.5%) had received ≥12 doses. Four subjects completed the study, and 867 subjects remained in the study. A total of 176 subjects were discontinued from the study, with the most common reasons being “subject’s withdrawal” (84 subjects) and “adverse events” (37 subjects). Table 42 shows the ApoE ε4 carrier status.

Table 42. ApoE ε4 carrier status (safety analysis set)

ApoE ε4 carrier status	Donanemab[a] (N = 1040)
Carrier	62.4 (649)
Homozygous	11.0 (114)
Heterozygous	51.4 (535)
Non-carrier	37.6 (391)

% (n)
[a] Missing data for 7 subjects

Table 43 shows the incidence of adverse events.

Table 43. Incidence of adverse events (safety analysis set)

	Donanemab (N = 1047)
Any adverse events	85.0 (890)
Common events[a]	
Amyloid related imaging abnormality-oedema/effusion	19.7 (206)
COVID-19	19.1 (200)
Amyloid related imaging abnormality-microhaemorrhages and haemosiderin deposits	16.5 (173)
Fall	12.7 (133)
Headache	12.0 (126)
Infusion related reaction	10.0 (105)
Urinary tract infection	6.3 (66)
Dizziness	5.9 (62)
Superficial siderosis of central nervous system	5.4 (57)

% (n)

[a] Adverse events occurring in ≥5% of subjects

Deaths occurred in 10 of 1,047 subjects (1.0%)during the study (thalamus haemorrhage, gun shot wound, pneumonia aspiration, acute respiratory failure, head injury, dysphagia, death, cardiac arrest, pelvic fracture, and respiratory failure in 1 subject each). Among these events, thalamus haemorrhage was considered related to the study drug. The incidence of serious adverse events was 17.3% (181 of 1,047 subjects). Serious adverse events occurring in ≥0.7% of subjects were syncope (1.1%), atrial fibrillation (1.0%), COVID-19 (0.8%), amyloid related imaging abnormality-oedema/effusion (0.7%), and transient ischaemic attack (0.7%). Among these, all the events of amyloid related imaging abnormality-oedema/effusion and syncope in 1 of the subjects, and transient ischaemic attack were considered related to the study drug.

Adverse events led to treatment discontinuation in 7.5% (79 of 1,047) of subjects. Those occurring in ≥0.5% of subjects were infusion related reaction (2.8%), amyloid related imaging abnormality-oedema/effusion (1.2%), and amyloid related imaging abnormality-microhaemorrhages and haemosiderin deposits (0.8%).

7.R Outline of the review conducted by PMDA

7.R.1 Clinical positioning of donanemab

The applicant's explanation about the clinical positioning of donanemab:

Alzheimer's disease, which is an age-related neurodegenerative disorder, begins with an asymptomatic stage (preclinical AD), followed by MCI, during which the patient can maintain activities of daily living independently. The disease then gradually progresses to mild, moderate, and finally to severe dementia. The clinical course of AD typically involves slowly progressive memory and learning impairment, starting from episodic memory impairment, followed by progression to aphasia, executive dysfunction, visuospatial dysfunction, personality change, and other social cognitive dysfunctions, and eventually, death due to comorbid illness (*Clinical Practice Guideline for Dementia*. 2017 [in Japanese] Igaku-Shoin Ltd.;2017:p204-5). Progressive cognitive impairment leading to loss of daily living activity independence in patients with AD imposes a significant burden on caregivers; therefore, AD is also an extremely serious disease from a socioeconomic perspective and needs to be addressed urgently.

Of AD medications approved in Japan, ChE inhibitors (donepezil, galantamine, and rivastigmine) and an *N*-methyl-D-aspartate (NMDA) receptor antagonist (memantine) are symptomatic drugs, which mitigate clinical symptoms by improving neurotransmission, but cannot slow the progression of the disease itself. Conversely, lecanemab, an approved anti-Aβ antibody, is a drug that can be used for the treatment of early AD. Lecanemab has been reported to slow AD progression and clinical decline (*N Engl J Med.* 2023;388:9-21) by removing brain Aβ plaques, one of the factors that cause AD (*Science.* 1992;256:184-5, *Science.* 2002;297:353-6).

As with lecanemab, donanemab is an anti-Aβ antibody that has been developed based on the amyloid hypothesis. Donanemab targets N3pG Aβ, which is present only in insoluble amyloid plaques, and is different from lecanemab in that it selectively acts on amyloid plaques. In addition, compared with lecanemab, which is administered every 2 weeks, donanemab has a longer dosing interval, every 4 weeks, with a shorter duration of administration for each dose. Therefore, donanemab can be selected as a treatment option considering the burden on both patients and caregivers.

The results for the primary endpoint (iADRS) and secondary endpoints (CDR-SB and other clinical symptoms) in the global phase III study (Study AACI), which was conducted in patients with early AD with low to high tau levels in the brain, suggest that donanemab can slow the progression of AD symptoms compared to placebo, showing similar effects regardless of patient characteristics [see Section "7.R.3.2 Factors affecting efficacy"]. In addition, donanemab clearly demonstrated its ability to reduce brain Aβ plaques [see Section "7.R.3.3 Biomarkers"]. It is considered that safety-related risks for donanemab including ARIA can be controlled irrespective of *APOE4* genotype [see Section "7.R.4 Safety"]. Furthermore, in principle, the duration of treatmentwith donanemab should be up to 18 months, and dosing can be ceased in ≤18 months if amyloid plaques have been removed [see Section "7.R.6 Dosage and administration"]. Therefore, the limited treatment duration may reduce not only the risk of adverse reactions that may result from extended treatment but also the burden on patients and their families and caregivers in association with medication cost and regular visits.

Based on the above, donanemab is expected to become a new treatment option for patients with early AD.

PMDA's view:
Donanemab is a monoclonal antibody targeting N3pG Aβ, which is considered to be present only in brain amyloid plaques. Donanemab is considered to exert its therapeutic effect by selectively binding to amyloid plaques to promote their removal [see Section "3.R Outline of the review conducted by PMDA"]. In the foreign phase II study (Study AACG) in patients with early AD with low or medium tau levels, the change from baseline in clinical endpoints such as iADRS at Week 76 supported the efficacy of donanemab to a certain extent, and amyloid PET scan showed a reduction in brain Aβ plaques in subjects treated with donanemab. Study AACI, which was a confirmatory study in patients with early AD with low to high tau levels, demonstrated the clinically meaningful efficacy of donanemab. Based on its benefits demonstrated in the study, donanemab has acceptable safety [see Sections "7.R.3 Efficacy" and "7.R.4 Safety"]. In view of the above results, it is meaningful to make donanemab available in clinical settings as a new option for the treatment of

patients with early AD because the drug product is different from the approved anti-Aβ antibody in terms of dosing interval and regimen. However, as described in Section 7.R.2 and subsequent sections, the applicant should ensure that healthcare professionals and patients are made aware of the increased risk of developing adverse reactions such as ARIA and infusion related reactions during treatment with donanemab, and of the need for periodical safety monitoring, such as by MRI. In addition, the applicant should clarify the intended patient population of donanemab and consider the criteria needed to decide as to whether to cease treatment with donanemab and the way in which such information should be provided.

7.R.2 Study AACI

7.R.2.1 Appropriateness of Japan's participation in Study AACI

The applicant's explanation about the appropriateness of Japan's participation in Study AACI, a global study:

Intrinsic ethnic factors

Study AACD, a phase I study in patients with early AD and moderate AD-D, showed that the PK parameters at steady state in Japanese patients receiving donanemab 20 mg/kg as an intravenous infusion every 4 weeks were similar to those in non-Japanese patients [see Section "6.R.1 Differences in PK between Japanese and non-Japanese populations"]. Study AACI adopted fixed dosage (1400 mg, however, 700 mg for the first 3 doses), as with Study AACG, a phase II study [see Section "7.R.6.1 Recommended dosage, dosing interval, and route of administration"]. Simulation was performed based on an ex post facto PPK analysis using data from the phase I through III studies, and the results confirmed that the PK parameters in Japanese patients receiving donanemab 1400 mg every 4 weeks did not differ markedly from those in non-Japanese patients [see Section "6.2.1.3 Population pharmacokinetic analysis"]. An Alzheimer's Disease Neuroimaging Initiative (ADNI) study conducted in patients with MCI to mild AD-D showed that the progression of AD symptoms was similar between Japanese and North American populations (*Alzheimers Dement.* 2018;14:1077-87).

Extrinsic ethnic factors

Guidelines both in Japan and in other countries recommend that the diagnosis of AD be made based on not only clinical symptoms but also clinical practice criteria that incorporate biomarkers reflecting AD pathology and genetic tests (*Clinical Practice Guideline for Dementia.* 2017 [in Japanese] Igaku-Shoin Ltd.;2017:p210-3, *Issues to Consider in the Clinical Evaluation and Development of Drugs for Alzheimer's Disease.* The University of Tokyo Hospital;2017:p4-7 [https://www.pmda.go.jp/files/000221584.pdf, last accessed on April 5, 2024]). There is no significant difference between Japan and other countries in this regard. As for AD medications, there is no difference in the availability of symptomatic AD drugs (ChE inhibitors and memantine) between Japan and other countries. At the time of initiation of Study AACI, no anti-Aβ antibodies had been approved. In Study AACI, patients who had been treated with an anti-Aβ antibody were not eligible for enrollment, and concomitant use of any anti-Aβ antibody under study was prohibited. Therefore, the efficacy and safety of donanemab are unlikely to have been affected by other anti-Aβ antibodies.

In view of the above, Japan's participation in the global study (Study AACI) is justifiable.

PMDA's view:

Even though the applicant's investigation into the differences in PK between Japanese and non-Japanese populations at the stage of designing Study AACI is insufficient, Japan's participation in Study AACI is justifiable, based on the applicant's explanation about the intrinsic and extrinsic factors as well as the results of simulation by the ex post facto PPK analysis.

7.R.2.2 Efficacy endpoints

The applicant's explanation about the details of selecting the efficacy endpoints in Study AACI and the rationale for the selection:

Before initiating a clinical study of donanemab, there were no established, high-sensitivity assessment scales to detect the progression of clinical symptoms in patients with early AD; accordingly, iADRS was developed.

The iADRS is an integrated scale that is composed of 31 items from ADAS-Cog13 (13 items) and ADCS-iADL (18 items) to assess both cognition and the ability to perform activities of daily living (*Neurol Clin Pract.* 2023;13:e200127). The iADRS is characterized by the following: (1) it is capable of capturing disease progression from MCI due to AD to moderate AD-D, and treatment effects on MCI due to AD and mild AD-D (e.g., *N Engl J Med.* 2018;378:321-30, *JAMA Neurol.* 2020;77:199-209); (2) clinically meaningful estimates of intraindividual variation[28)] are defined (*Alzheimers Dement*. [N Y] 2022a;8:e12312); and (3) it is associated with therapeutically important outcomes, such as caregivers' burden and patients' quality of life (QOL), is presented (*J Alzheimers Dis.* 2022b;88:577-88). These factors suggest that iADRS is a scale that assesses the progression of clinical symptoms in patients with early AD in an appropriate manner from the perspectives of both cognitive function as well as daily activity function.

Study AACI was initially designed as a phase II study with CDR-SB as the primary endpoint and iADRS as a secondary endpoint. However, based on the results from the foreign phase II study (Study AACG), the applicant decided to conduct Study AACI as a confirmatory study to verify the reproducibility of the results from Study AACG. Accordingly, the endpoints were also changed to iADRS as the primary endpoint and CDR-SB as a key secondary endpoint (Protocol [version (b)] [dated on February 17, 2021]).

PMDA's view:

Because patients with early AD include those with mild cognitive impairment or a mild degree of impairment in daily activities who have relatively gradual progression of symptoms, the applicant's strategy to use assessment scales that can capture early symptomatic changes as the primary endpoint is reasonable. Currently, no assessment scales that can evaluate the efficacy of drugs for early AD (clinical significance of intervention) have been established. Data have suggested that iADRS, the integrated assessment scale developed by the applicant, may be suitable for the evaluation of efficacy in the disease stage earlier than AD-D compared with conventional endpoints used in clinical studies in patients with AD-D. However, given the scarcity of actual use of iADRS in clinical studies, a general consensus has not been achieved regarding the

[28)] Five-point decrease from baseline for subjects with a diagnosis of MCI due to AD (MMSE score ≥27), and a 9-point decrease from baseline for subjects with a diagnosis of mild AD-D (MMSE score of 20-26).

clinical significance of the assessment results with iADRS. For these reasons, the efficacy of donanemab should be evaluated in a comprehensive manner by using not only iADRS but also other clinical assessment scales including CDR-SB, as well as biomarkers such as amyloid PET in Centiloids.

7.R.2.3 Appropriateness of study subjects

The criteria based on Clinical Dementia Rating Scale-Global Score (CDR-GS) were not incorporated into the eligibility criteria for Study AACI, and several subjects with baseline MMSE <20, defined as moderate AD were included in the study. In addition, Study AACI enrolled subjects with tau levels measured by tau PET using flortaucipir (^{18}F) only.

The applicant's explanation about the appropriateness of subjects enrolled in Study AACI:
In Study AACI, the eligibility criteria for cognitive impairment include gradual and progressive change in memory function reported by the subject or the study partner for ≥6 months, and an MMSE score ≥20 and ≤28 at screening (Visit 1) or earlier during the lead-in period (Visit 601). Because the baseline MMSE score was evaluated at the time of randomization (Visit 2), there were subjects whose MMSE score changed after screening. As a result, 143 subjects in the placebo group and 111 subjects in the donanemab group had baseline MMSE <20. However, only a small number of subjects were classified as having moderate dementia (CDR-GS 2) according to the CDR-GS disease classification at baseline, with 25 subjects (2.9%) in the placebo group and 25 subjects (3.0%) in the donanemab group. To avoid entry bias and regression toward the mean, Study AACI employed a design in which the above MMSE criteria is applied at screening instead of baseline to minimize problems that might arise in the comparison of treatment effect between the groups.

In Study AACI, to evaluate the efficacy of donanemab during the 76-week evaluation period, the eligibility criteria based on tau PET scans using flortaucipir (^{18}F) were employed to enroll patients with early AD with low to high tau levels in the brain who were expected to experience disease progression during the efficacy evaluation period.

Based on the above, the applicant considers that the eligibility criteria for Study AACI are appropriate to evaluate the efficacy of donanemab in patients with early AD.

PMDA's view:
Given that donanemab was developed for the treatment of patients with early AD, it would have been more logical to establish eligibility criteria whereby patients with early AD were selected using CDR-GS at the time of enrollment in Study AACI. However, according to the applicant's explanation, in Study AACI, the number of subjects whose CDR-GS disease class defined as moderate AD-D at baseline was small, and the majority of subjects were considered to have early AD. Therefore, the study results have been obtained from the intended patient population for donanemab. The criteria for tau PET were used to facilitate the detection of difference from placebo in efficacy in Study AACI, while they also limit the patient population in whom efficacy was demonstrated. It should be noted that the results obtained in in the limited population may not

be generalized. The intended patient population for donanemab will be discussed in a separate section, taking the study results into account [see Section "7.R.5 Intended patient population and indication of donanemab"].

7.R.3 Efficacy

7.R.3.1 Significance of results from clinical studies

The applicant's explanation about the significance of results from the clinical studies of donanemab:
In Study AACG in patients with early AD with low or medium tau levels in the brain, the donanemab group showed a statistically significantly less decline for the change from baseline in iADRS at Week 76, the primary endpoint, compared to the placebo group (Table 26). The results for secondary endpoints including CDR-SB showed consistent trends toward less decline in the donanemab group compared to the placebo group (Table 27).

In Study AACI in patients with early AD with low to high tau levels in the brain, the donanemab group showed a statistically significant less decline for the change from baseline in iADRS at Week 76, the primary endpoint, compared to the placebo group, and the results were consistent between the overall population and the low-medium tau population (Table 33 and Figure 2), confirming the reproducibility of the efficacy of donanemab demonstrated in Study AACG. The results for secondary endpoints, including CDR-SB, also showed consistent trends toward less decline in the donanemab group compared to the placebo group (Table 34 and Figure 2). The rates of slowing declines in iADRS and in CDR-SB in the donanemab group in Study AACI (difference from placebo in change from baseline in iADRS [or CDR-SB] / change from baseline in iADRS [or CDR-SB] in the placebo group × 100) were 22.3% (iADRS) and 28.9% (CDR-SB) for the overall population and 35.1% (iADRS) and 36.0% (CDR-SB) for the low-medium tau population, all of which were greater than the clinically significant value of 20% (*Alzheimers Dement.* 2023;19:2730-6). Furthermore, the time-progression model with repeated measures (Time-PMRM) (*Stat Med.* 2022;41:5537-57)[29)] was used to estimate the slowing of disease progression at Week 76 in the donanemab group compared to the placebo group in the overall population and low-medium tau population. The time saved for disease progression as assessed by iADRS was 1.38 months (overall) and 4.36 months (low-medium tau) and that as assessed by CDR-SB was 5.44 months (overall) and 7.53 months (low-medium tau).

[29)] A model with baseline and post-baseline endpoint measurements at the scheduled visits as dependent variables, with baseline age, baseline symptomatic AD medication (ChE inhibitor and/or memantine) use, pooled site, and baseline tau category (low-medium or high) as covariates. In the analysis with the low-medium tau population, baseline tau level was removed from the model.

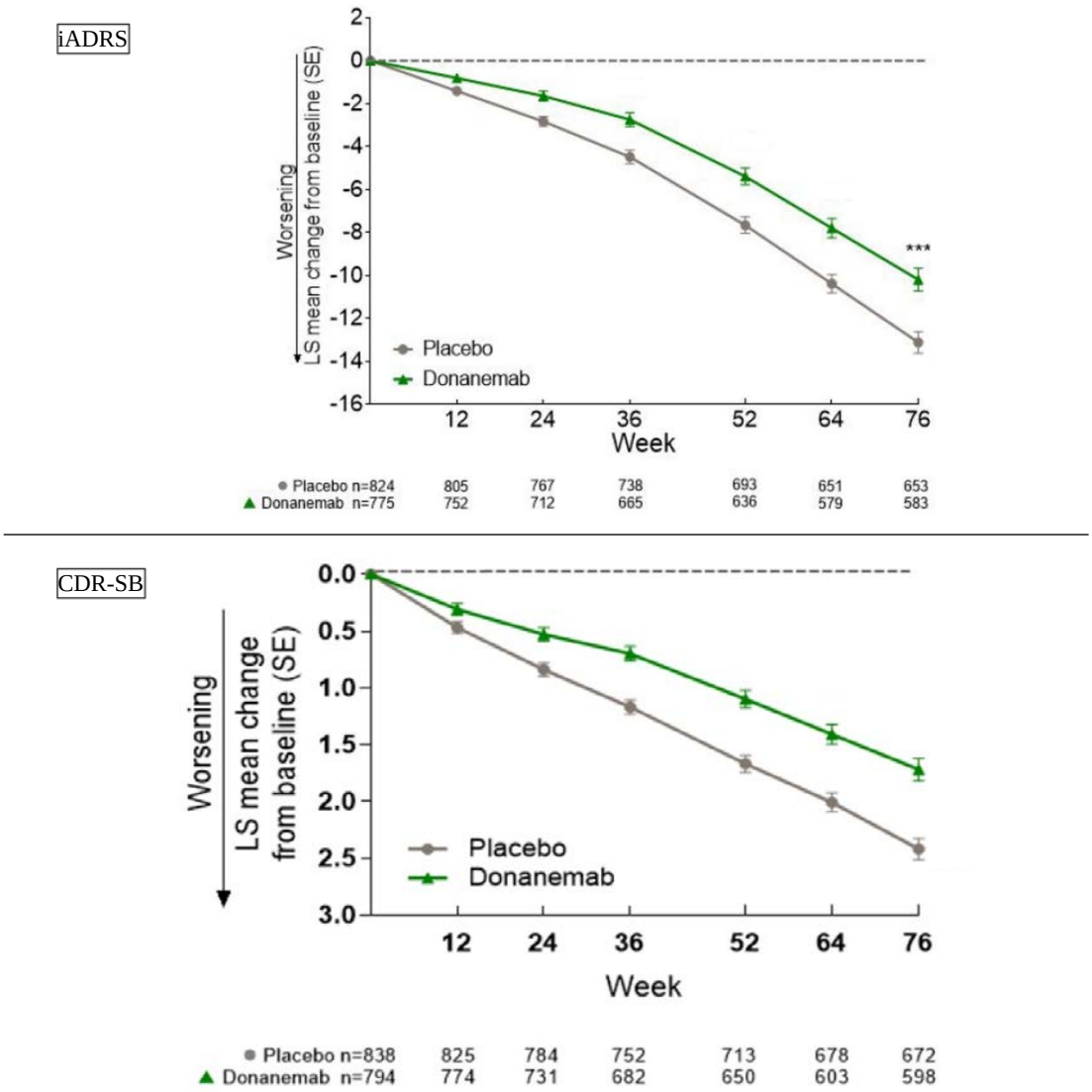


Figure 2. Change in iADRS and CDR-SB over time in the overall population in Study AACI (EES)

The minimal clinically important difference (MCID) in iADRS was −5 points for MCI due to AD and −9 points for mild AD-D, while the MCID in CDR-SB was 1 point for MCI due to AD and 2 points for mild AD-D (*Alzheimers Dement.* [N Y] 2022;8:e12312). In Study AACI, the disease progression at Week 76 was evaluated by defining decline from baseline in iADRS or CDR-SB by MCID as described above or worse[30)] as a disease progression event. Table 44 shows the hazard ratio for donanemab versus placebo. The results suggested a decreased risk of disease progression in the donanemab group compared to the placebo group based on the MCID.

[30)] Worsening at 2 consecutive visits. The MCID was determined based on the clinical status at screening.

Table 44. Disease progression (first onset) events based on MCID during the double-blind period in Study AACI (EES)

		Overall population		Low-medium tau population	
		Placebo	Donanemab	Placebo	Donanemab
iADRS	Incidence[a]	39.6 (329/831)	29.4 (232/788)	33.6 (190/565)	23.8 (129/542)
	Hazard ratio [two-sided 95% CI][b]	—	0.700 [0.582, 0.842]	—	0.640 [0.506, 0.810]
CDR-SB	Incidence[a]	41.2 (348/844)	28.4 (229/805)	36.8 (211/573)	23.4 (130/555)
	Hazard ratio [two-sided 95% CI][b]	—	0.623 [0.519, 0.748]	—	0.595 [0.473, 0.748]

[a] % (n/N)

[b] A Cox proportional hazards model (baseline age, baseline value, and baseline symptomatic AD medication [ChE inhibitor and/or memantine] use as covariates, stratified by pooled site and baseline brain tau category [low-medium or high]). In the analysis with the low-medium tau population, baseline brain tau category was removed from the stratification factors.

Disease progression[31)] (first onset) events to the next or more advanced stage at Week 76 as measured by CDR-GS in the donanemab group were compared with those in the placebo group using the Cox proportional hazards model. The hazard ratio (donanemab vs. placebo) [two-sided 95% confidence interval (CI)] was 0.626 [0.510, 0.769] for the overall population and 0.614 [0.471, 0.800] for the low-medium tau population.

Figure 3 shows the distribution of change from baseline in iADRS and CDR-SB in each subject at Week 76 in the overall population by treatment group in Study AACI. In the donanemab group, the proportion of subjects whose iADRS or CDR-SB improved or worsened to a lesser degree tended to be higher in the donanemab group than in the placebo group.

31) Worsening in CDR-GS from baseline at 2 consecutive visits was defined as a clinical worsening event.

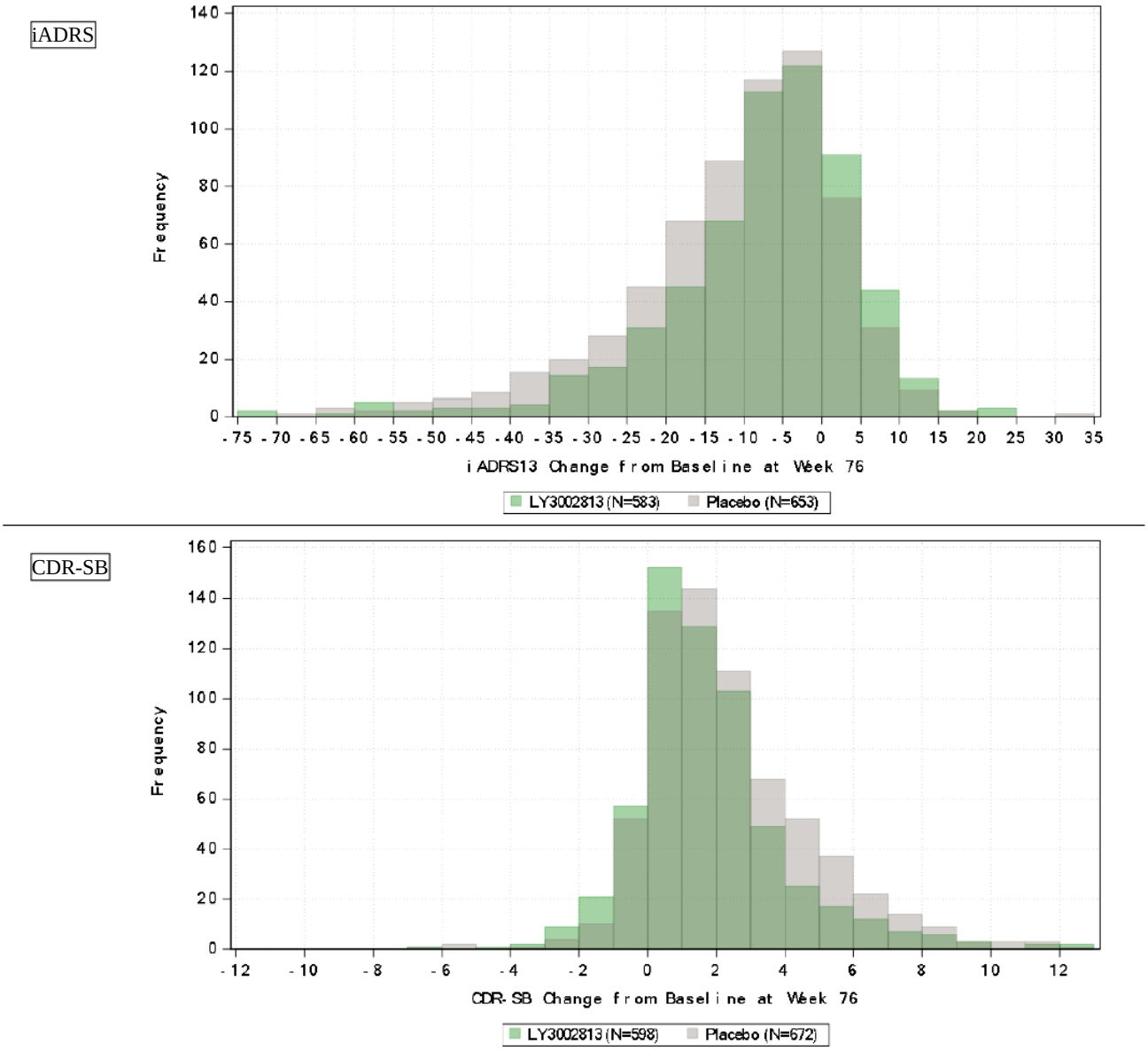


Figure 3. Distribution of change from baseline in iADRS and CDR-SB in each subject at Week 76 in the overall population by treatment group in Study AACI (EES) (LY3002813 is donanemab)

Furthermore, unlike symptomatic medications, donanemab demonstrated enhanced effects over time rather than soon after treatment initiation in Study AACI (Figure 2); therefore, the results suggest sustained slowing of disease progression as a clinical effect.

In view of the above, the results from the clinical studies of donanemab show that donanemab have meaningful effects in slowing clinical decline in patients with early AD.

PMDA's view:

The results presented by the applicant and the following points suggest that the efficacy of donanemab in the treatment of patients with early AD has been demonstrated:

- Since the symptoms of AD progress gradually over an extended period, slowing of disease progression by 20% to 30% at an early stage is considered of some significance in terms of the slowing of iADRS and CDR-SB decline.
- In Study AACI, donanemab slowed disease progression to a certain extent, suggesting that donanemab may slow the progression from MCI due to AD to AD-D, or from mild AD-D to moderate or severe AD-D.
- The results for ADAS-Cog13 and ADCS-iADL, secondary endpoints, support the efficacy of donanemab in cognition and activities of daily living in patients with early AD.

PMDA's view on the disease-modifying effect of donanemab:
Study AACG and Study AACI have demonstrated that donanemab can slow the progression of clinical symptoms such as cognitive impairment, and the results as measured by biomarkers that was possibly related to AD pathology in the donanemab group were more favorable than those in the placebo group. However, as discussed later in Section "7.R.3.3 Biomarkers," changes in clinical symptoms were not clearly correlated with the change in biomarkers; and neigther of the studies was designed to assess the disease-modifying effects of donanemab as the primary evaluation; therefore, current data are not sufficient to conclude that the disease-modifying effects of donanemab have been verified.

The appropriateness of the decision above will be finalized taking into account the comments from the Expert Discussion.

7.R.3.2 Factors affecting efficacy

The applicant's explanation about the factors affecting the efficacy of donanemab:
The results of subgroup analysis on the change from baseline in iADRS and CDR-SB at Week 76 in Study AACI by brain tau level are presented in Tables 45 and 46, respectively. The between-group difference in change from baseline in iADRS in the high tau population was 1.26, with a slowing rate of 6.0%, which showed a trend toward slowing of decline, although the extent of slowing is small compared to the overall population. The between-group difference in change from baseline in CDR-SB was −0.69, with a slowing rate of 20.8%. Given that the results did not differ markedly from those for the overall population, donanemab is also expected to be effective in the high tau population.

Table 45. Change from baseline in iADRS at Week 76 in Study AACI by brain tau (EES)

	Overall population		Low-medium tau population		High tau population	
	Placebo	Donanemab	Placebo	Donanemab	Placebo	Donanemab
Baseline[a]	103.82 ± 13.88 (N = 824)	104.55 ± 13.90 (N = 775)	105.95 ± 13.42 (N = 560)	105.92 ± 13.72 (N = 533)	99.27 ± 13.81 (N = 263)	101.51 ± 13.83 (N = 242)
Week 76[a]	93.82 ± 20.38 (N = 653)	96.98 ± 20.87 (N = 583)	98.88 ± 17.95 (N = 444)	101.31 ± 18.23 (N = 418)	83.13 ± 21.12 (N = 208)	86.01 ± 23.06 (N = 165)
Change from baseline (NCS2)[b, c]	−13.11 ± 0.50	−10.19 ± 0.53	−9.27 ± 0.49	−6.02 ± 0.50	−20.76 ± 1.05	−19.51 ± 1.14
Between-group difference [two-sided 95% CI]	—	2.92 [1.508, 4.331]	—	3.25 [1.883, 4.618]	—	1.26 [−1.770, 4.282]

[a] Mean ± standard deviation

[b] An NCS2 model with basis expansion terms (2 terms), NCS basis expansion term (2 terms)-by-treatment interaction, baseline age, pooled site, baseline brain tau category (low-medium or high), and baseline symptomatic AD medication (ChE inhibitor and/or memantine) use as fixed effects. In the analyses with the low-medium tau population and high tau population, baseline brain tau category was removed from the model. An unstructured variance-covariance matrix was used for within-subject effects.

[c] Least squares mean ± standard error

Table 46. Change from baseline in CDR-SB at Week 76 in Study AACI by brain tau (EES)

	Overall population		Low-medium tau population		High tau population	
	Placebo	Donanemab	Placebo	Donanemab	Placebo	Donanemab
Baseline[a]	3.89 ± 2.034 (N = 838)	3.92 ± 2.055 (N = 794)	3.64 ± 1.986 (N = 569)	3.72 ± 2.088 (N = 546)	4.43 ± 2.036 (N = 268)	4.36 ± 1.913 (N = 248)
Week 76[a]	5.80 ± 3.223 (N = 672)	5.25 ± 3.207 (N = 598)	5.13 ± 2.929 (N = 459)	4.64 ± 2.903 (N = 424)	7.24 ± 3.370 (N = 212)	6.75 ± 3.421 (N = 174)
Change from baseline (MMRM)[b, c]	2.42 ± 0.092	1.72 ± 0.096	1.88 ± 0.102	1.20 ± 0.105	3.34 ± 0.180	2.64 ± 0.190
Between-group difference [two-sided 95% CI]	—	−0.70 [−0.95, −0.45]	—	−0.67 [−0.95, −0.40]	—	−0.69 [−1.19, −0.20]

[a] Mean ± standard deviation

[b] An MMRM with treatment, visit, treatment-by- visit interaction, baseline value, baseline value-by-visit interaction, baseline age, pooled site, baseline brain tau category (low-medium or high), and baseline symptomatic AD medication (ChE inhibitor and/or memantine) use as fixed effects. In the analyses with the low-medium tau population and high tau population, baseline brain tau category was removed from the model. An unstructured variance-covariance matrix was used for within-subject effects.

[c] Least squares mean ± standard error

Subgroup analyses were performed for factors other than brain tau category. Table 47 shows the results of subgroup analyses by baseline symptomatic AD medication (ChE inhibitor and/or memantine) use, disease stage, ApoE ε4 carrier status, baseline amyloid PET Centiloids, and baseline tau PET SUVr The results indicated no significant difference between each subgroup and the overall population. In addition, similar subgroup analyses were performed for several factors including age, sex, and region, and the results indicated no significant difference between each subgroup and the overall population.

Table 47. Change from baseline in iADRS and CDR-SB at Week 76 in Study AACI by baseline symptomatic AD medication use, disease stage, ApoE ε4 carrier status, baseline amyloid PET Centiloids, and baseline tau PET SUVr (EES)

		Time point	Change in iADRS (NCS2)[a, c]		Between-group difference[b, c]	Change in CDR-SB (NCS2)[a, c]		Between-group difference[b, c]
			Placebo	Donanemab		Placebo	Donanemab	
Overall population		BL	N = 824	N = 775	—	N = 838	N = 794	—
		76	−13.11 ± 0.50	−10.19 ± 0.53	2.92	2.33 ± 0.09	1.66 ± 0.09	−0.67
Symptomatic AD medication	Not used	BL	N = 322	N = 306	—	N = 325	N = 309	—
		76	−9.62 ± 0.80	−8.42 ± 0.83	1.20	1.86 ± 0.14	1.25 ± 0.14	−0.61
	Used	BL	N = 502	N = 469	—	N = 513	N = 485	—
		76	−15.33 ± 0.64	−11.32 ± 0.67	4.02	2.63 ± 0.11	1.92 ± 0.11	−0.71
Disease stage	MCI (MMSE ≥27)	BL	N = 120	N = 131	—	N = 122	N = 134	—
		76	−5.44 ± 1.23	−3.30 ± 1.20	2.14	0.94 ± 0.21	0.65 ± 0.20	−0.29
	Mild AD-D (MMSE ≥20 and <26)	BL	N = 493	N = 468	—	N = 503	N = 477	—
		76	−11.74 ± 0.62	−9.49 ± 0.64	2.25	2.09 ± 0.10	1.41 ± 0.11	−0.68
	Moderate AD-D (MMSE <20)	BL	N = 210	N = 174	—	N = 211	N = 177	—
		76	−20.92 ± 0.98	−17.22 ± 1.12	3.70	3.74 ± 0.17	3.07 ± 0.19	−0.68
ApoE ε4 carrier status	Carrier	BL	N = 588	N = 538	—	N = 600	N = 554	—
		76	−11.80 ± 0.58	−9.38 ± 0.62	2.42	2.20 ± 0.10	1.55 ± 0.11	−0.66
	Homozygous	BL	N = 139	N = 127	—	N = 143	N = 131	—
		76	−10.91 ± 1.20	−9.90 ± 1.27	1.01	2.28 ± 0.20	1.88 ± 0.22	−0.41
	Heterozygous	BL	N = 449	N = 411	—	N = 457	N = 423	—
		76	−12.08 ± 0.67	−9.20 ± 0.70	2.87	2.17 ± 0.12	1.44 ± 0.12	−0.73
	Non-carrier	BL	N = 234	N = 235	—	N = 236	N = 238	—
		76	−16.30 ± 0.92	−11.74 ± 0.94	4.57	2.65 ± 0.16	1.89 ± 0.16	−0.76
Baseline amyloid PET Centiloids	<84.96	BL	N = 274	N = 257	—	N = 284	N = 261	−
		76	−11.26 ± 0.89	−9.90 ± 0.92	1.35	2.17 ± 0.15	1.70 ± 0.16	−0.47
	≥84.96 and ≤115	BL	N = 289	N = 246	—	N = 290	N = 254	—
		76	−13.48 ± 0.85	−11.36 ± 0.93	2.13	2.36 ± 0.15	1.73 ± 0.16	−0.63
	>115	BL	N = 261	N = 272	—	N = 264	N = 279	—
		76	−14.49 ± 0.87	−9.49 ± 0.88	5.00	2.45 ± 0.15	1.55 ± 0.15	−0.91
Baseline tau PET SUVr	<1.1797	BL	N = 253	N = 247	—	N = 255	N = 251	—
		76	−5.84 ± 0.82	−4.89 ± 0.83	0.95	1.44 ± 0.15	0.88 ± 0.15	−0.56
	≥1.1797 and ≤1.4049	BL	N = 257	N = 248	—	N = 262	N = 257	—
		76	−11.50 ± 0.80	−6.42 ± 0.82	5.08	2.01 ± 0.14	1.27 ± 0.15	−0.74
	>1.4049	BL	N = 261	N = 245	—	N = 267	N = 248	—
		76	−20.63 ± 0.79	−18.86 ± 0.84	1.76	3.41 ± 0.14	2.92 ± 0.15	−0.49

BL = Baseline; 76 = Week 76

[a] Least squares mean ± standard error

[b] Least squares mean

[c] An NCS2 model with treatment, basis expansion terms (2 terms), subgroup factor, subgroup factor-by-treatment interaction, subgroup factor-by-basis expansion terms (2 terms) interaction, baseline age, pooled site, baseline brain tau category (low-medium or high), and baseline symptomatic AD medication (ChE inhibitor and/or memantine) use as fixed effects. If a subgroup factor is included as a factor in the fixed effect, the model was adjusted as necessary. An unstructured variance-covariance matrix was used for within-subject effects.

In view of the above discussions, no factors that may have a clear impact on the efficacy of donanemab have been identified.

PMDA's view:

Based on the results of subgroup analyses of factors that may affect the efficacy of donanemab, and the applicant's explanation, donanemab can be expected to have efficacy in the treatment of patients with early AD who meet the eligibility criteria for Study AACI, irrespective of brain tau level (low, medium, or high), symptomatic AD medication use, disease stage (MCI due to AD or mild AD-D), ApoE ε4 carrier status, and baseline amyloid PET Centiloids.

The efficacy of donanemab in patients with early AD having no or very low tau and the efficacy of donanema by geographic region will be discussed in Sections "7.R.5 Intended patient population and indication of donanemab" and "7.R.3.4 Efficacy in Japanese patients."

7.R.3.3 Biomarkers

The applicant's explanation about the relationships between the change in biomarkers and clinical assessment scales in Study AACI:

(a) Amyloid PET

The change from baseline in brain Aβ plaques at Week 76 as measured by the amyloid PET Centiloid scale in Study AACI was −0.67 and −87.03 in the placebo and donanemab groups, respectively. While no clear change from baseline has been detected in the placebo group, the brain Aβ plaque at Week 76 in the donanemab group was 14.95, which was lower than the level corresponding to amyloid negativity by visual read (24.1[32)]) (Table 35). Table 48 shows the change from baseline in accumulated Aβ levels in the brain over time.

Table 48. Change from baseline in brain Aβ plaques over time as measured by amyloid PET Centiloid scale in Study AACI (EES, overall population)

	Placebo	Donanemab		
		Overall population	Subgroup of subjects who met dose cessation criteria at Week 24	Subgroup of subjects who met dose cessation criteria at Week 52
Baseline[a]	101.75 ± 34.371 (N = 812)	104.02 ± 34.417 (N = 765)	80.72 ± 25.640 (N = 130)	98.32 ± 31.690 (N = 195)
Change from baseline at Week 24 (MMRM)[b]	0.07 ± 0.859	−62.95 ± 0.883	−83.19 ± 0.849	−69.50 ± 0.891
Between-group difference [two-sided 95% CI]	—	−63.03 [−65.36, −60.69]	—[c]	—[c]
Change from baseline at Week 52 (MMRM)[b]	−1.02 ± 0.890	−83.05 ± 0.922	−85.72 ± 1.071	−95.66 ± 0.609
Between-group difference [two-sided 95% CI]	—	−82.02 [−84.46, −79.59]	—[c]	—[c]
Change from baseline at Week 76 (MMRM)[b]	−0.67 ± 0.909	−87.03 ± 0.950	−82.90 ± 1.079	−94.87 ± 0.787
Between-group difference [two-sided 95% CI]	—	−86.37 [−88.87, −83.87]	—[c]	—[c]

[a] Mean ± standard deviation
[b] Least squares mean ± standard error (An MMRM with treatment, visit, treatment-by-visit interaction, baseline value, baseline value-by-visit interaction, baseline age, and baseline brain tau categroy [low-medium or high] as fixed effects. An unstructured variance-covariance matrix was used for within-subject effects.)
[c] Not calculated.

Table 49 shows the proportion of subjects who achieved amyloid plaque clearance (<24.1 Centiloids; the same applies hereinafter) over time in Study AACI. The proportion of subjects who achieved amyloid plaque clearance was higher in the donanemab group than in the placebo group at all the timepoints, i.e., Weeks 24, 52, and 76.

[32)] Amyloid levels <24.1 Centiloids represents conditions of pathologically absent or sparse neuritic plaque, and are classified as being amyloid-negative on PET by visual read (*Alzheimer's & Dementia.* 2018:14;1565-71).

Table 49. The proportion of subjects who achieved amyloid plaque clearance over time in Study AACI (EES, overall population)

	Placebo (N = 812)	Donanemab (N = 765)
Week 24	0.2 (2/805)	29.7 (226/761)
Week 52	0.1 (1/730)	66.1 (443/670)
Week 76	0.3 (2/690)	76.4 (469/614)

% (n/N)

(b) Tau PET

It is known that the frontal lobe is one of the main regions in which tau deposition is observed in association with the progressive stage of AD (*Alzheimers Dement.* [Amst] 2018;10:221-31). Table 50 shows the change from baseline at Week 76 in tau PET frontal SUVr, with flortaucipir (^{18}F) as a PET tracer, in Study AACI.

Table 50. Change from baseline at Week 76 in tau PET frontal SUVr in Study AACI (EES, overall population)

	Placebo	Donanemab
Baseline[a]	1.2738 ± 0.27962 (N = 654)	1.2775 ± 0.28772 (N = 578)
Change from baseline at Week 76 (ANCOVA)[b, c]	0.0442 ± 0.00374	0.0401 ± 0.00398
Between-group difference [two-sided 95% CI]	—	−0.0041 [−0.0148, 0.0066]

[a] Mean ± standard deviation; subjects with baseline and at least 1 post-baseline measurement were analyzed.
[b] Least squares mean ± standard error
[c] An ANCOVA model with baseline, baseline brain tau level (low-medium or high), baseline age, and treatment as factors.

(c) Plasma biomarkers

Table 51 shows the change over time from baseline in plasma levels of p-tau217, p-tau181, glial fibrillary acidic protein (GFAP), and neurofilament light chain (NfL) in Study AACI. Plasma p-tau217, p-tau181, and GFAP decreased in the donanemab group compared to the placebo group. Plasma NfL increased from baseline both in the donanemab and placebo groups.

Table 51. Change over time from baseline in plasma levels p-tau217, p-tau181, GFAP, and NfL in Study AACI (EES, overall population)

		Placebo	Donanemab
p-tau217	Baseline[a]	0.66 ± 0.295 (N = 786)	0.67 ± 0.304 (N = 758)
	Change from baseline at Week 24 (MMRM)[b, c]	0.01 ± 0.007	−0.15 ± 0.007
	Between-group difference [two-sided 95% CI]	—	−0.16 [−0.18, −0.14]
	Change from baseline at Week 52 (MMRM)[b, c]	0.02 ± 0.008	−0.20 ± 0.008
	Between-group difference [two-sided 95% CI]	—	−0.21 [−0.24, −0.19]
	Change from baseline at Week 76 (MMRM)[b, c]	0.03 ± 0.008	−0.19 ± 0.009
	Between-group difference [two-sided 95% CI]	—	−0.22 [−0.24, −0.20]
p-tau181	Baseline[a]	1.59 ± 0.149 (N = 813)	1.60 ± 0.163 (N = 774)
	Change from baseline at Week 24 (MMRM)[b, c]	0.02 ± 0.004	−0.06 ± 0.004
	Between-group difference [two-sided 95% CI]	—	−0.08 [−0.09, −0.07]
	Change from baseline at Week 52 (MMRM)[b, c]	0.02 ± 0.004	−0.08 ± 0.004
	Between-group difference [two-sided 95% CI]	—	−0.10 [−0.11, −0.09]
	Change from baseline at Week 76 (MMRM)[b, c]	0.02 ± 0.004	−0.08 ± 0.004
	Between-group difference [two-sided 95% CI]	—	−0.11 [−0.12, −0.10]
GFAP	Baseline[a]	2.43 ± 0.203 (N = 824)	2.44 ± 0.223 (N = 783)
	Change from baseline at Week 24 (MMRM)[b, c]	0.03 ± 0.005	−0.05 ± 0.005
	Between-group difference [two-sided 95% CI]	—	−0.08 [−0.10, −0.07]
	Change from baseline at Week 52 (MMRM)[b, c]	0.03 ± 0.005	−0.10 ± 0.005
	Between-group difference [two-sided 95% CI]	—	−0.14 [−0.15, −0.12]
	Change from baseline at Week 76 (MMRM)[b, c]	0.05 ± 0.005	−0.09 ± 0.006
	Between-group difference [two-sided 95% CI]	—	−0.14 [−0.15, −0.12]
NfL	Baseline[a]	1.31 ± 0.180 (N = 824)	1.31 ± 0.191 (N = 783)
	Change from baseline at Week 24 (MMRM)[b, c]	0.03 ± 0.004	0.06 ± 0.005
	Between-group difference [two-sided 95% CI]	—	0.02 [0.01, 0.04]
	Change from baseline at Week 52 (MMRM)[b, c]	0.05 ± 0.005	0.04 ± 0.005
	Between-group difference [two-sided 95% CI]	—	−0.01 [−0.02, 0.00]
	Change from baseline at Week 76 (MMRM)[b, c]	0.05 ± 0.005	0.05 ± 0.006
	Between-group difference [two-sided 95% CI]	—	−0.01 [−0.02, 0.01]

[a] Common log-transformed value, mean ± standard deviation
[b] Common log-transformed value, least squares mean ± standard error
[c] An MMRM with treatment, visit, treatment-by-visit interaction, baseline value, baseline value-by-visit interaction, baseline age, and baseline brain tau category (low-medium or high) as fixed effects. An unstructured variance-covariance matrix was used for within-subject effects.

(d) Relationships between biomarkers and clinical assessment scales

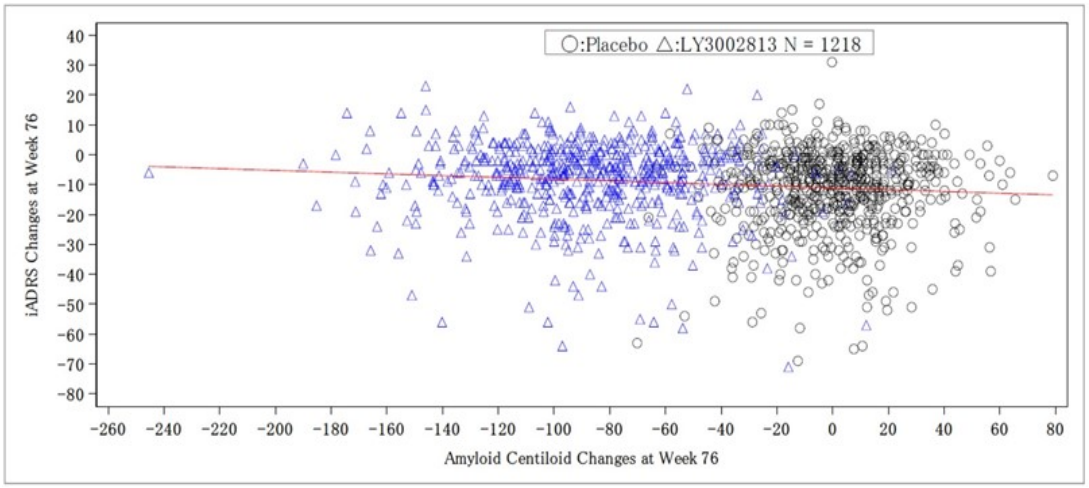
Table 52 shows the subject-level correlation between the change from baseline in the amyloid PET Centiloid scale and change from baseline in iADRS or CDR-SB at Week 76 in Study AACI, and Figure 4 shows scatter plots for the changes. However, the interpretation of these results requires caution becasue (1) the baseline amyloid level may affect the clinical progression rate and (2) values are not adjusted for variables that may affect the clinical change.

Table 52. Subject-level correlation between the change from baseline in the amyloid PET Centiloid scale and change from baseline in iADRS or CDR-SB at Week 76 in Study AACI (EES, overall population)

	iADRS		CDR-SB	
	Placebo	Donanemab	Placebo	Donanemab
Correlation between change from baseline in Aβ PET at Week 24 and change from baseline in iADRS or CDR-SB at Week 76	0.0154	−0.0713	−0.0703	0.0224
Correlation between change from baseline in Aβ PET at Week 52 and change from baseline in iADRS or CDR-SB at Week 76	0.0176	−0.0533	0.0063	0.0259
Correlation between change from baseline in Aβ PET at Week 76 and change from baseline in iADRS or CDR-SB at Week 76	−0.0187	−0.0382	0.0117	0.0211

Spearman's partial correlation coefficients (adjusted by baseline age and clinical assessment scale)

iADRS



CDR-SB

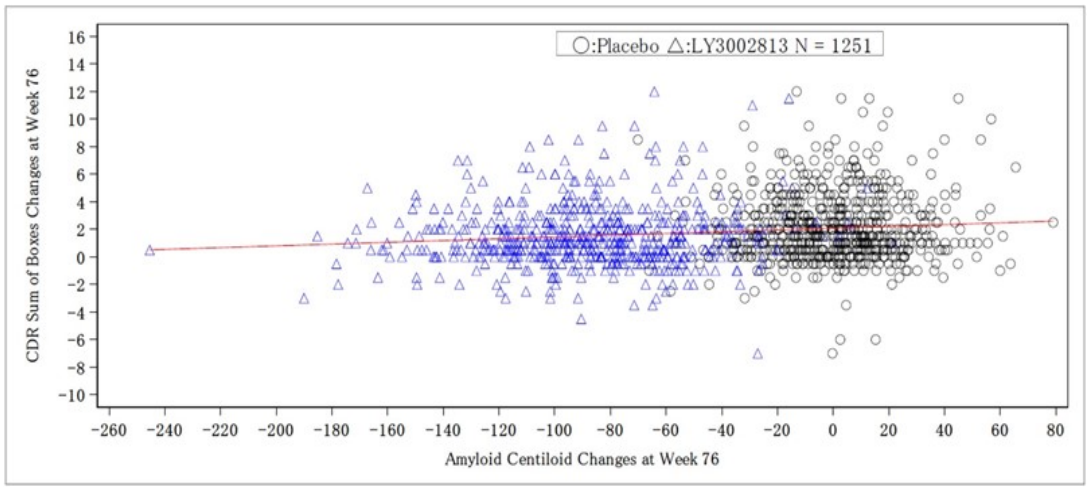


Figure 4. Scatter plots for the changes from baseline in amyloid PET Centiloid scale and changes from baseline in iADRS and in CDR-SB in Study AACI (EES, overall population) (LY3002813 is donanemab)

On the basis of the investigations in Subsections (a) through (d) above, the applicant considers that donanemab exerts its disease-modifying effect by directly removing amyloid pathology and slowing the progression of AD, including tau pathology downstream of amyloid pathology and neurodegeneration.

PMDA's view:

Changes in biomarkers in Study AACI can be interpreted to indicate that the effects of donanemab on biomarkers are considered to be related to AD pathology in humans. Such effects include brain Aβ plaque reduction as measured by amyloid PET, that is predictable from the mechanism of action of donanemab. However, there were no clear correlations between the brain Aβ plaque as measured by amyloid PET and changes in the clinical symptoms, and therefore, the clinical therapeutic effect of donanemab cannot be determined based on the change from baseline in any of the biomarkers evaluated in Study AACI [for the PMDA's conclusion on the disease-modifying effect, see Section "7.R.3.1 Significance of results from clinical studies"].

The appropriateness of the above conclusions by PMDA will be finalized taking into account the comments from the Expert Discussion.

7.R.3.4 Efficacy in Japanese patients

The applicant's explanation about the efficacy in the Japanese population (43 subjects in the placebo group and 45 subjects in the donanemab group)[33)]:

The results for the primary endpoint (iADRS) and secondary endpoints (CDR-SB, ADAS-Cog13, and ADCS-iADL) in the Japanese population were consistent with the results for the overall population, except for CDR-SB in the low-medium tau Japanese population, in Study AACI, showing a trend toward less decline in the donanemab group compared to the placebo group [see Section "7.4 Global phase III study"]. The CDR-SB results in the low-medium tau Japanese population were considered to be attributable to an extremely high baseline score (≥10) in the placebo group and great improvement (≥5) in 2 subjects on placebo during the study period in this subgroup. The brain Aβ plaque in the donanemab group was reduced compared to the placebo group in the Japanese population, and this was a result consistent with the overall population. Based on the above, The efficacy of donanemab demonstrated in the overall population can be promising in the Japanese population.

PMDA's view:

The efficacy of donanemab is supported by the results of Study AACI showing that there was a difference from placebo in the change from baseline in iADRS in the Japanese population. Based on the comprehensive efficacy evaluation, the efficacy of donanemab demonstrated in the overall population can be promising in the Japanese population.

7.R.4 Safety

On the basis of the incidence of adverse events in the clinical studies, and results of discussions in the following subsections, as well as the efficacy of donanemab demonstrated in Section "7.R.3 Efficacy," PMDA concluded

33) Based on the results of Study AACG, if 100 of 1,000 subjects in the low-medium tau population were assumed to be Japanese, the consistency (defined as the ratio [difference from placebo in Japanese subjects / difference from placebo in the overall population] ≥0.5 at the final timepoint) of results between the Japanese and overall populations for iADRS, the primary endpoint, could be confirmed with a probability of approximately 77%. Accordingly, a target sample size of 100 Japanese subjects in the low-medium tau population (total of 150 Japanese subjects) was planned and 88 Japanese subjects were enrolled.

that donanemab has clinically acceptable safety in patients with early AD with low to high tau levels. Note that the safety evaluation in this section is based on the pooled data from the following populations in addition to the results from Study AACG, Study AACI (double-blind and extension periods), and Study AACI Addendum 9.

- Placebo-controlled safety analysis population (Dona-PC): an integrated population from Study AACG and Study AACI (double-blind period)
- Integrated safety analysis population (All-Dona): donanemab-treated integrated population from Study AACG, Study AACH Part B (an open-label extension study of Study AACG), Study AACI (double-blind and extension periods), Study AACI Addendum 9, and Study AACN (foreign phase III study in patients with early AD)

7.R.4.1 Amyloid-related imaging abnormalities

Amyloid-related imaging abnormalities (ARIAs) are abnormal radiographic findings in the brain of patients treated with an anti-Aβ antibody, and are classified into two types: ARIA-E and ARIA-H. Although the underlying mechanism of ARIA has not been clarified, published literature has reported that ARIA may be caused by the breakdown of accumulated Aβ plaques in the cerebral blood vessels leading to increased vascular permeability, and the breakdown of cerebral parenchymal Aβ that inhibits perivascular clearance and contributes to perivascular inflammation (*J Prev Alz Dis.* 2022;2:211-20). Given that any irreversible brain damage induced by ARIA-E or ARIA-H may have a serious impact on the prognosis of patients, including cognition, PMDA asked the applicant to explain about the patient monitoring for risk reduction and actions required in the event of detecting ARIA.

The applicant's explanation is presented in the subsections below:

(a) Incidence of ARIA-E and ARIA-H

The applicant's explanation about the incidence of ARIA-E and ARIA-H in the clinical studies of donanemab:
Table 53 shows the incidence of ARIA-E in Study AACG, Study AACI (double-blind period), Study AACI (including the extension period), and Study AACI Addendum 9. The majority of the first-onset ARIA-E in the donanemab group occurred within 24 weeks after the start of treatment with donanemab. Among subjects with ARIA-E in the donanemab group in Study AACG and Study AACI (double-blind period), those who experienced the resolution of ARIA-E on MRI were assessed. The median time to resolution of ARIA-E [Min, Max] was 59 days [15, 292].

Table 53. Incidence of ARIA-E in Study AACG, Study AACI (double-blind period), Study AACI (including extension period), and Study AACI Addendum 9 (safety analysis set)

	AACG		AACI (double-blind period)		AACI (including extension period)		AACI Addendum 9
	Placebo (N = 125)	Donanemab (N = 131)	Placebo (N = 874)	Donanemab (N = 853)	Placebo-donanemab[a] (N = 570)	Donanemab-donanemab[b] (N = 568)	Donanemab (N = 1047)
Incidence of ARIA-E	0.8 (1)	26.7 (35)	2.1 (18)	24.0 (205)	8.8 (50)	21.5 (122)	19.7 (206)
Details of ARIA-E events[c]							
Severity on MRI[d]							
Mild	0 (0)	31.4 (11)	72.2 (13)	28.3 (58)	34.0 (17)	32.8 (40)	38.3 (79)
Moderate	100.0 (1)	45.7 (16)	22.2 (4)	63.4 (130)	54.0 (27)	64.8 (79)	54.9 (113)
Severe	0 (0)	20.0 (7)	0 (0)	6.8 (14)	10.0 (5)	2.5 (3)	6.8 (14)
Suspected or missing	0 (0)	2.9 (1)	5.6 (1)	1.5 (3)	2.0 (1)	0 (0)	0 (0)
Presence of symptoms							
Asymptomatic ARIA-E	0 (0)	85.7 (30)	100.0 (18)	74.6 (153)	80.0 (40)	80.3 (98)	79.6 (164)
Symptomatic ARIA-E	100.0 (1)	14.3 (5)	0 (0)	25.4 (52)	20.0 (10)	19.7 (24)	20.4 (42)
Recurrence[e]	0 (0)	11.4 (4)	0 (0)	24.9 (51)	4.0 (2)	28.7 (35)	21.4 (44)
Serious events	0 (0)	5.7 (2)	0 (0)	6.3 (13)	4.0 (2)	0 (0)	3.4 (7)
Events leading to death	0 (0)	0 (0)	0 (0)	0.5 (1)	0 (0)	0 (0)	0 (0)
Events leading to treatment discontinuation[f]	100.0 (1)	20.0 (7)	16.7 (3)	10.2 (21)	6.0 (3)	0 (0)	6.3 (13)
Outcome[g]							
Resolved	0 (0)	91.4 (32)	61.1 (11)	91.2 (187)	94.0 (47)	91.0 (111)	95.6 (197)
Not resolved	100.0 (1)	8.6 (3)	38.9 (7)	8.8 (18)	6.0 (3)	9.0 (11)	4.4 (9)
Time to the first ARIA-E in each treatment period[e]							
≤4 weeks	0 (0)	5.7 (2)	0 (0)	4.4 (9)	34.0 (17)	2.5 (3)	13.1 (27)
>4 weeks and ≤12 weeks	0 (0)	54.3 (19)	11.1 (2)	48.8 (100)	48.0 (24)	47.5 (58)	49.6 (96)
>12 weeks and ≤16 weeks	100.0 (1)	8.6 (3)	0 (0)	5.4 (11)	2.0 (1)	5.7 (7)	1.0 (2)
>16 weeks and ≤24 weeks	0 (0)	11.4 (4)	38.9 (7)	29.3 (60)	14.0 (7)	28.7 (35)	29.6 (61)
>24 weeks and ≤36 weeks	0 (0)	11.4 (4)	0 (0)	4.4 (9)	0 (0)	6.6 (8)	2.9 (6)
>36 weeks and ≤52 weeks	0 (0)	8.6 (3)	22.2 (4)	5.9 (12)	0 (0)	7.4 (9)	5.3 (11)
>52 weeks	0 (0)	0 (0)	22.2 (4)	0.5 (1)	0 (0)	1.6 (2)	1.5 (3)
Missing	0 (0)	0 (0)	5.6 (1)	1.5 (3)	2.0 (1)	0 (0)	0 (0)
Time to resolution of the first ARIA-E in each treatment period[e]							
≤12 weeks after onset	0 (0)	65.7 (23)	44.4 (8)	67.3 (138)	22.0 (11)	75.4 (92)	71.4 (147)
>12 weeks and ≤20 weeks after onset	0 (0)	22.9 (8)	11.1 (2)	20.5 (42)	6.0 (3)	20.5 (25)	18.4 (38)
>20 weeks after onset	100.0 (1)	11.4 (4)	5.6 (1)	8.8 (18)	6.0 (3)	3.3 (4)	7.3 (15)
Not resolved	0 (0)	0 (0)	33.3 (6)	2.0 (4)	64.0 (32)	0.8 (1)	2.9 (6)
Missing[h]	0 (0)	0 (0)	5.6 (1)	1.5 (3)	2.0 (1)	0 (0)	0 (0)

% (n)

[a] Results in the extension period for all subjects receiving placebo in the double-blind period and treated with donanemab in the extension period.

[b] Results in the double-blind and extension periods for all subjects treated with donanemab in the double-blind and extension periods.

[c] The incidences in this row and subsequent rows were calculated using the number of subjects with ARIA-E events as the denominator.

[d] The severity on MRI was assessed based on the maximum severity of an ARIA-E event on MRI. However, the severity for the "suspected or missing" category was based on MRI or TEAE cluster. For this reason, the "suspected or missing" category comprises subjects with "suspected" severity of events on MRI, and subjects whose MRI scan results were "missing" but whose TEAE cluster indicated ARIA.

[e] Based on MRI

[f] Based on TEAE cluster

[g] When all recorded episodes based on MRI "resolved," and all recorded episodes based on TEAE cluster "recovered or resolved," the outcome was reported as "resolved." For all other cases, the outcome was reported as "not resolved."

[h] In each treatment period, the time to resolution of the first ARIA-E was assessed based on the onset of ARIA-E on MRI; therefore, subjects who developed only TEAE cluster-based ARIA-E were included in the "missing" category.

Table 54 shows the incidence of ARIA-H in Study AACG, Study AACI (double-blind period), Study AACI (including the extension period), and Study AACI Addendum 9. The majority of events occurred within 24 weeks of the start of treatment with donanemab.

Table 54. Incidence of ARIA-H in Study AACG, Study AACI (double-blind period), Study AACI (including the extension period), and Study AACI Addendum 9 (safety analysis set)

	AACG		AACI (double-blind period)		AACI (including extension period)		AACI Addendum 9
	Placebo (N = 125)	Donanemab (N = 131)	Placebo (N = 874)	Donanemab (N = 853)	Placebo-donanemab[a] (N = 570)	Donanemab-donanemab[b] (N = 568)	Donanemab (N = 1047)
Incidence of ARIA-H	8.8 (11)	30.5 (40)	13.6 (119)	31.4 (268)	13.3 (76)	34.5 (196)	25.1 (263)
Details of ARIA-H[c]							
Incidence by subcategory							
Cerebral microhemorrhage[d]	4.8 (6)	19.8 (26)	11.8 (103)	25.8 (220)	11.9 (68)	29.0 (165)	20.8 (218)
Superficial siderosis[d]	2.4 (3)	17.6 (23)	2.9 (25)	15.7 (134)	5.6 (32)	14.4 (82)	11.3 (118)
Cerebral hemorrhage[d]	0 (0)	0 (0)	0.2 (2)	0.4 (3)	0.2 (1)	0.2 (1)	0.3 (3)
Details of ARIA-H events							
Severity on MRI[e]							
Mild	72.7 (8)	50.0 (20)	77.3 (92)	47.0 (126)	55.3 (42)	56.6 (111)	60.8 (160)
Moderate	9.1 (1)	17.5 (7)	14.3 (17)	19.4 (52)	15.8 (12)	15.3 (30)	12.9 (34)
Severe	0 (0)	32.5 (13)	5.0 (6)	33.2 (89)	28.9 (22)	27.6 (54)	25.9 (68)
Suspected or missing	18.2 (2)	0 (0)	3.4 (4)	0.4 (1)	0 (0)	0.5 (1)	0.4 (1)
Presence of symptoms							
Asymptomatic ARIA-H	100.0 (11)	100.0 (40)	97.5 (116)	96.3 (258)	98.7 (75)	97.4 (191)	99.2 (261)
Symptomatic ARIA-H	0 (0)	0 (0)	2.5 (3)	3.7 (10)	1.3 (1)	2.6 (5)	0.8 (2)
Recurrence[f]	18.2 (2)	25.0 (10)	26.9 (32)	40.3 (108)	9.2 (7)	41.3 (81)	32.7 (86)
Serious events	0 (0)	0 (0)	0 (0)	1.5 (4)	0 (0)	0 (0)	1.1 (3)
Events leading to death	0 (0)	0 (0)	0 (0)	0.1 (1)	0 (0)	0 (0)	0 (0)
Events leading to study drug treatment discontinuation[g]	9.1 (1)	30.0 (12)	2.5 (3)	3.7 (10)	1.3 (1)	0.5 (1)	4.2 (11)
Time to the first ARIA-H in each treatment period[f]							
≤4 weeks	9.1 (1)	7.5 (3)	5.9 (7)	1.1 (3)	39.5 (30)	0.5 (1)	10.3 (27)
>4 weeks and ≤12 weeks	18.2 (2)	42.5 (17)	24.4 (29)	33.6 (90)	43.4 (33)	25.5 (50)	35.0 (92)
>12 weeks and ≤16 weeks	9.1 (1)	5.0 (2)	2.5 (3)	6.3 (17)	2.6 (2)	5.1 (10)	6.8 (18)
>16 weeks and ≤24 weeks	0 (0)	15.0 (6)	23.5 (28)	29.9 (80)	10.5 (8)	26.5 (52)	27.8 (73)
>24 weeks and ≤36 weeks	9.1 (1)	15.0 (6)	1.7 (2)	6.0 (16)	1.3 (1)	7.7 (15)	3.4 (9)
>36 weeks and ≤52 weeks	0 (0)	7.5 (3)	18.5 (22)	14.9 (40)	2.6 (2)	16.3 (32)	13.3 (35)
>52 weeks	36.4 (4)	7.5 (3)	20.2 (24)	7.8 (21)	0 (0)	17.9 (35)	3.0 (8)
Missing[h]	18.2 (2)	0 (0)	3.4 (4)	0.4 (1)	0 (0)	0.5 (1)	0.4 (1)

% (n)

[a] Results in the extension period for all subjects receiving placebo in the double-blind period and treated with donanemab in the extension period.

[b] Results in the double-blind and extension periods for all subjects treated with donanemab in the double-blind and extension periods.

[c] The incidences in this row and subsequent rows were calculated using the number of subjects with ARIA-H events as the denominator.

[d] Based on MRI. Cerebral hemorrhage was not included in the ARIA-H.

[e] The severity on MRI was assessed based on the maximum severity of an ARIA-H event on MRI. However, the severity for the "suspected or missing" category was based on MRI or TEAE cluster. For this reason, the "suspected or missing" category comprises subjects with "suspected" severity of events on MRI, and subjects whose MRI scan results were "missing" but whose TEAE cluster indicated ARIA.

[f] Based on MRI

[g] Based on TEAE cluster

[h] In each treatment period, the time to resolution of the first ARIA-H was assessed based on the onset of ARIA-H on MRI; therefore, subjects who developed only TEAE cluster-based ARIA-H were included in the "missing" category.

Table 55 shows the severity of symptomatic ARIA and its associated symptoms[34)] reported in Study AACG, Study AACI (double-blind period), Study AACI (including extension period), and Study AACI Addendum 9.

[34)] When ARIA-H is concurrent with ARIA-E, it is difficult to differentiate the symptoms of ARIA-H from those of ARIA-E, and therefore, the symptoms associated with symtomatic ARIA-H were not collected in a systematic manner. For this reason, the severity of symptomatic ARIA and its associated symptoms were analyzed regardless of ARIA-E or ARIA-H.

Table 55. Severity of symptomatic ARIA and its associated symptoms reported in Study AACG, Study AACI (double-blind period), Study AACI (including extension period), and Study AACI Addendum 9 (safety analysis set)

	AACG		AACI (double-blind period)		AACI (including extension period)		AACI Addendum 9
	Placebo (N = 125)	Donanemab (N = 131)	Placebo (N = 874)	Donanemab (N = 853)	Placebo-donanemab[a] (N = 570)	Donanemab-donanemab[b] (N = 568)	Donanemab (N = 1047)
Incidence of ARIA-E or ARIA-H	9.6 (12)	38.2 (50)	14.9 (130)	36.8 (314)	15.1 (86)	39.8 (226)	30.1 (315)
Incidence of symptomatic ARIA[c]	8.3 (1)	10.0 (5)	0 (0)	16.6 (52)	11.6 (10)	10.6 (24)	13.3 (42)
Details of symptomatic ARIA events							
Clinical severity[d]							
Mild	0 (0)	0 (0)	0 (0)	9.6 (30)	7.0 (6)	9.3 (21)	8.3 (26)
Moderate	0 (0)	0 (0)	0 (0)	3.8 (12)	4.7 (4)	1.3 (3)	4.4 (14)
Severe	0 (0)	0 (0)	0 (0)	3.2 (10)	0 (0)	0 (0)	0.6 (2)
Missing	8.3 (1)	10.0 (5)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Common symptoms associated with ARIA							
Headache	8.3 (1)	2.0 (1)	0 (0)	7.6 (24)	7.0 (6)	6.6 (15)	8.6 (27)
Confusional state	0 (0)	0 (0)	0 (0)	4.1 (13)	1.2 (1)	1.8 (4)	2.5 (8)
Dizziness	8.3 (1)	0 (0)	0 (0)	1.3 (4)	2.3 (2)	0.9 (2)	1.0 (3)
Seizure	0 (0)	0 (0)	0 (0)	1.3 (4)	0 (0)	0.4 (1)	0.6 (2)
Nausea	0 (0)	0 (0)	0 (0)	1.3 (4)	0 (0)	0.4 (1)	0.3 (1)
Gait disturbance	0 (0)	0 (0)	0 (0)	1.0 (3)	0 (0)	0 (0)	1.6 (5)
Fatigue	0 (0)	0 (0)	0 (0)	1.0 (3)	0 (0)	0.4 (1)	0.6 (2)
Tremor	0 (0)	0 (0)	0 (0)	1.0 (3)	0 (0)	0 (0)	0.3 (1)

% (n)

[a] Results in the extension period for all subjects receiving placebo in the double-blind period and treated with donanemab in the extension period.

[b] Results in the double-blind and extension periods for all subjects treated with donanemab in the double-blind and extension periods.

[c] The incidences in this row and subsequent rows were calculated using the number of subjects with ARIA-E or ARIA-H events as the denominator.

[d] In Study AACG, data on the severity of symptomatic ARIA were not collected.

The tables below show the incidence of ARIA-E and ARIA-H by ApoE ε4 carrier status (carrier or non-carrier) and *APOE4* genotype (heterozygous or homozygous carriers) in Study AACI (double-blind period) (Table 56) and in Study AACI (including the extension period) (Table 57). The incidence of ARIA-E and ARIA-H was highest in ApoE ε4 homozygous carriers, followed by ApoE ε4 heterozygous carriers, and then ApoE ε4 non-carriers. The incidence of severe ARIA-E and ARIA-H on MRI tended to be higher in ApoE ε4 carriers than in ApoE ε4 non-carriers.

Table 56. Incidence of ARIA-E and ARIA-H by ApoE ε4 carrier status and *APOE4* genotype in Study AACI (double-blind period) (safety analysis set)

	Placebo			Donanemab		
	ApoE ε4 carriers		ApoE ε4 non-carriers (N = 250)	ApoE ε4 carriers		ApoE ε4 non-carriers (N = 255)
	Homozygous (N = 146)	Heterozygous (N = 474)		Homozygous (N = 143)	Heterozygous (N = 452)	
Incidence of ARIA-E	3.4 (5)	2.1 (10)	0.8 (2)	41.3 (59)	23.2 (105)	15.7 (40)
Details of ARIA-E events						
Severity on MRI[a, b]						
Mild	60.0 (3)	80.0 (8)	100.0 (2)	23.7 (14)	28.6 (30)	32.5 (13)
Moderate	40.0 (2)	10.0 (1)	0 (0)	67.8 (40)	61.0 (64)	65.0 (26)
Severe	0 (0)	0 (0)	0 (0)	6.8 (4)	8.6 (9)	2.5 (1)
Suspected or missing	0 (0)	10.0 (1)	0 (0)	1.7 (1)	1.9 (2)	0 (0)
Presence of symptoms[a]						
Asymptomatic ARIA-E	100.0 (5)	100.0 (10)	100.0 (2)	79.7 (47)	71.4 (75)	75.0 (30)
Symptomatic ARIA-E	0 (0)	0 (0)	0 (0)	20.3 (12)	28.6 (30)	25.0 (10)
Incidence of ARIA-H	20.5 (30)	12.9 (61)	11.2 (28)	50.3 (72)	32.5 (147)	18.8 (48)
Details of ARIA-H events						
Severity on MRI[a, b]						
Mild	73.3 (22)	77.0 (47)	82.1 (23)	33.3 (24)	46.3 (68)	68.8 (33)
Moderate	16.7 (5)	14.8 (9)	10.7 (3)	18.1 (13)	23.8 (35)	8.3 (4)
Severe	10.0 (3)	1.6 (1)	7.1 (2)	48.6 (35)	29.3 (43)	22.9 (11)
Suspected or missing	0 (0)	6.6 (4)	0 (0)	0 (0)	0.7 (1)	0 (0)
Presence of symptoms[a]						
Asymptomatic ARIA-H	96.7 (29)	98.4 (60)	96.4 (27)	97.2 (70)	95.2 (140)	97.9 (47)
Symptomatic ARIA-H	3.3 (1)	1.6 (1)	3.6 (1)	2.8 (2)	4.8 (7)	2.1 (1)
Details of symptomatic ARIA events						
Clinical severity[a]						
Symptomatic and mild	0 (0)	0 (0)	0 (0)	7.5 (6)	10.0 (17)	11.1 (7)
Symptomatic and moderate	0 (0)	0 (0)	0 (0)	3.8 (3)	4.1 (7)	3.2 (2)
Symptomatic and severe	0 (0)	0 (0)	0 (0)	3.8 (3)	3.5 (6)	1.6 (1)
Missing	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

% (n)

[a] The incidences were calculated using the number of subjects with ARIA-E events, ARIA-H events, or ARIA-E or ARIA-H events as the denominator.

[b] The severity on MRI was assessed based on the maximum severity on MRI. However, the severity for the "suspected or missing" category was based on MRI or TEAE cluster. For this reason, the "suspected or missing" category comprises subjects with "suspected" severity of events on MRI, and subjects whose MRI scan results were "missing" but whose TEAE cluster indicated ARIA.

Table 57. Incidence of ARIA-E and ARIA-H by ApoE ε4 carrier status and *APOE4* genotype in Study AACI (including the extension period)

	Placebo-donanemab[a]			Donanemab-donanemab[b]		
	ApoE ε4 carriers		ApoE ε4 non-carriers (N = 166)	ApoE ε4 carriers		ApoE ε4 non-carriers (N = 179)
	Homozygous (N = 107)	Heterozygous (N = 297)		Homozygous (N = 91)	Heterozygous (N = 298)	
Incidence of ARIA-E	12.1 (13)	8.4 (25)	7.2 (12)	38.5 (35)	21.1 (63)	13.4 (24)
Details of ARIA-E events						
Severity on MRI[c, d]						
Mild	30.8 (4)	36.0 (9)	33.3 (4)	34.3 (12)	30.2 (19)	37.5 (9)
Moderate	46.2 (6)	56.0 (14)	58.3 (7)	65.7 (23)	65.1 (41)	62.5 (15)
Severe	15.4 (2)	8.0 (2)	8.3 (1)	0 (0)	4.8 (3)	0 (0)
Suspected or missing	7.7 (1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Presence of symptoms						
Asymptomatic ARIA-E	69.2 (9)	88.0 (22)	75.0 (9)	85.7 (30)	77.8 (49)	79.2 (19)
Symptomatic ARIA-E	30.8 (4)	12.0 (3)	25.0 (3)	14.3 (5)	22.2 (14)	20.8 (5)
Incidence of ARIA-H	18.7 (20)	13.1 (39)	10.2 (17)	51.6 (47)	36.6 (109)	22.3 (40)
Details of ARIA-H events						
Severity on MRI[c, d]						
Mild	35.0 (7)	64.1 (25)	58.8 (10)	42.6 (20)	55.0 (60)	77.5 (31)
Moderate	20.0 (4)	10.3 (4)	25.5 (4)	12.8 (6)	21.1 (23)	2.5 (1)
Severe	45.0 (9)	25.6 (10)	17.6 (3)	44.7 (21)	22.9 (25)	20.0 (8)
Suspected or missing	0 (0)	0 (0)	0 (0)	0 (0)	0.9 (1)	0 (0)
Presence of symptoms						
Asymptomatic ARIA-H	95.0 (19)	100.0 (39)	100.0 (17)	95.7 (45)	98.2 (107)	97.5 (39)
Symptomatic ARIA-E	5.0 (1)	0 (0)	0 (0)	4.3 (2)	1.8 (2)	2.5 (1)
Details of symptomatic ARIA events						
Clinical severity[c]						
Symptomatic and mild	9.1 (2)	4.3 (2)	11.1 (2)	7.5 (4)	10.6 (13)	8.0 (4)
Symptomatic and moderate	9.1 (2)	2.2 (1)	5.6 (1)	1.9 (1)	0.8 (1)	2.0 (1)
Symptomatic and severe	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Missing	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

% (n)

[a] Results in the extension period for all subjects receiving placebo in the double-blind period and treated with donanemab in the extension period.

[b] Results in the double-blind and extension periods for all subjects treated with donanemab in the double-blind and extension periods.

[c] The incidences were calculated using the number of subjects with ARIA-E events, ARIA-H events, or ARIA-E or ARIA-H events as the denominator.

[d] The severity on MRI was based on the maximum severity on MRI. However, the severity for the "suspected or missing" category was based on MRI or TEAE cluster. For this reason, the "suspected or missing" category comprises subjects with "suspected" severity of events on MRI, and subjects whose MRI scan results were "missing" but whose TEAE cluster indicated ARIA.

Table 58 shows the time to the first ARIA-E or ARIA-H by ApoE ε4 carrier status and *APOE4* genotype (heterozygous or homozygous) in Dona-PC. The majority of the first ARIA-E and ARIA-H events occurred within 24 weeks of the start of treatment with donanemab, irrespective of ApoE ε4 carrier status.

Table 58. Time to the first ARIA-E or ARIA-H by ApoE ε4 carrier status and *APOE4* genotype in Dona-PC

	Placebo			Donanemab		
	ApoE ε4 carriers		ApoE ε4 non-carriers (N = 282)	ApoE ε4 carriers		ApoE ε4 non-carriers (N = 291)
	Homozygous (N = 174)	Heterozygous (N = 538)		Homozygous (N = 168)	Heterozygous (N = 522)	
Time to the first ARIA-E						
Incidence of ARIA-E	6 subjects	10 subjects	2 subjects	70 subjects	126 subjects	43 subjects
Week ≤24[a]	66.7 (4)	50.0 (5)	0 (0)	85.7 (60)	85.7 (108)	90.7 (39)
Week >24[a]	33.3 (2)	40.0 (4)	100.0 (2)	12.9 (9)	12.7 (16)	9.3 (4)
Time to onset of the first ARIA-H						
Incidence of ARIA-H	34 subjects	66 subjects	30 subjects	90 subjects	162 subjects	55 subjects
Week ≤24[b]	55.9 (19)	51.5 (34)	60.0 (18)	67.8 (61)	71.6 (116)	72.7 (40)
Week >24[b]	41.2 (14)	40.9 (27)	40.0 (12)	32.2 (29)	27.8 (45)	27.3 (15)

% (n)

[a] The incidences were calculated using the number of subjects with ARIA-E events as the denominator.

[b] The incidences were calculated using the number of subjects with ARIA-H events as the denominator.

Table 59 shows the list of donanemab-treated subjects who developed serious ARIA-E in Study AACG, Study AACH Part B, Study AACI (double-blind period), Study AACI (extension period), and Study AACI Addendum 9. Serious ARIA-E occurred in 13 subjects in the donanemab group in Study AACI (double-blind period), 2 of whom died subsequently. The majority of serious ARIA-E resolved after dose interruption or discontinuation of donanemab.

Table 59. List of donanemab-treated subjects who developed serious ARIA-E in Study AACG, Study AACH Part B, Study AACI (double-blind period), Study AACI (extension period), and Study AACI Addendum 9 (safety analysis set)

	Treatment group	MCI /AD	Age (years)	Sex	Race	ApoE ε4 carrier status	Onset (Day)	Clinical severity	ARIA-H[a]	Donanemab disposition	Clinical outcome of ARIA-E	Related
AACG	Donanemab	MCI	7	[redacted]		Heterozygous	52	Severe	Yes	Discontinued	Resolved	Yes
	Donanemab	AD	7			Homozygous	73	Severe	Yes	Discontinued	Resolved	Yes
AACH Part B	Placebo[b]	AD	8			Homozygous	52	Severe	Yes	Discontinued	Resolved	Yes
	Placebo[b]	AD	8			Non-carrier	238	Mild	Yes	Interrupted	Resolving	No
	Placebo[b]	AD	7			Homozygous	74	Moderate	Yes	Interrupted	Resolved	Yes
AACI (double-blind)	Donanemab	AD	7			Heterozygous	427	Severe	Yes	Continued	Unknown[c]	Yes
	Donanemab	AD	6			Homozygous	19	Severe	Yes	Discontinued	Resolved	Yes
	Donanemab	MCI	8			Heterozygous	40	Moderate	No	Continued	Resolved	Yes
	Donanemab	AD	7			Non-carrier	17	Severe	Yes	Continued	Resolved	Yes
	Donanemab	AD	6			Heterozygous	121	Moderate	Yes	Discontinued	Resolved	Yes
	Donanemab	AD	7			Heterozygous	46	Severe	Yes	Continued	Resolved	Yes
	Donanemab	MCI	7			Homozygous	57	Severe	No	Discontinued	Resolving	Yes
	Donanemab	MCI	7			Heterozygous	45	Severe	Yes	Discontinued	Sequelae	Yes
	Donanemab	AD	7			Heterozygous	30	Severe	No	Discontinued	Resolving	Yes
	Donanemab	AD	6			Homozygous	79	Severe	Yes	Discontinued	Resolved	Yes
	Donanemab	AD	6			Homozygous	29	Mild	Yes	Interrupted	Resolved	Yes
	Donanemab	AD	6			Heterozygous	113	Severe	Yes	Discontinued	Resolved	Yes
	Donanemab	AD	7			Heterozygous	66	Severe	No	Discontinued	Death	Yes
AACI (extension)	Placebo[b]	AD	7			Homozygous	21[d]	Moderate	No	Discontinued	Resolved	Yes
	Placebo[b]	AD	8			Heterozygous	78[d]	Severe	Yes	Interrupted	Resolving	Yes
AACI Addendum 9	Donanemab	MCI	6			Homozygous	146	Severe	Yes	Interrupted	Resolved	Yes
	Donanemab	AD	7			Homozygous	56	Severe	Yes	Continued	Resolved	Yes
	Donanemab	MCI	7			Non-carrier	131	Moderate	No	Discontinued	Resolved	Yes
	Donanemab	AD	8			Heterozygous	48	Severe	Yes	Discontinued	Sequelae	Yes
	Donanemab	MCI	7			Unknown	32	Severe	Yes	Discontinued	Resolved	Yes
	Donanemab	MCI	7			Homozygous	75	Moderate	Yes	Discontinued	Resolved	Yes
	Donanemab	AD	6			Non-carrier	64	Severe	Yes	Discontinued	Resolved	Yes

[a] Based on MRI or TEAE cluster
[b] The treatment group in Study AACG or Study AACI (double-blind period)
[c] Died on Day 447. The cause was classified as "death," which was considered related to the study drug.
[d] Number of days after the start of the extension period

Table 60 shows the list of donanemab-treated subjects who developed cerebral hemorrhage[35)] in Study AACI (double-blind period), Study AACI (extension period), and Study AACI Addendum 9. Table 61 shows the summary of events in a subject who developed cerebral hemorrhage and hemorrhagic stroke[36)] on the same day as the onset of serious ARIA-H and died subsequently. This subject's data are not included in Table 60. No cerebral hemorrhage was reported in Study AACG.

35) Based on MRI or TEAE cluster
36) Because cerebral hemorrhage and hemorrhagic stroke were reported as ARIA-H, these events were not included in Table 60.

Table 60. List of donanemab-treated subjects who developed cerebral hemorrhage[35)] in Study AACI (double-blind period), Study AACI (extension period), and Study AACI Addendum 9 (safety analysis set)

	PT	Treatment group	MCI /AD	Age (years)	Sex	Race	ApoE ε4 carrier status	Onset (Day)	Concomitant antithrombotic use[a]	Severity	Bleeding site	Donanemab disposition	Clinical outcome of cerebral hemorrhage	Related
AACI (double-blind)	Cerebral haemorrhage	Donanemab	AD	7[redacted]	[redacted]	[redacted]	Heterozygous	192	Nonaspirin antiplatelet	Moderate	Occipital lobe	Discontinued	Resolving	Yes
	Cerebral haemorrhage	Donanemab	AD	8[redacted]	[redacted]	[redacted]	Heterozygous	526	None	Moderate	Parietal lobe	Interrupted	Not resolved	Yes
	Haemorrhagic stroke	Donanemab	MCI	7[redacted]	[redacted]	[redacted]	Heterozygous	33	None	Moderate	Occipital lobe	Continued	Resolved	Yes
	Haemorrhagic stroke							33	None	Severe	Occipital lobe	Discontinued	Resolved	Yes
	Haemorrhagic stroke							149	None	Moderate	Occipital lobe	Continued	Not resolved	Yes
AACI (extension)	—[b]	Placebo[c]	AD	6[redacted]	[redacted]	[redacted]	Homozygous	157[d]	None	—	Frontal lobe	—	—	—
	Cerebral haemorrhage	Placebo[c]	MCI	7[redacted]	[redacted]	[redacted]	Homozygous	25[d]	None	Mild	—	Interrupted	Not resolved	Yes
AACI Addendum 9	—[b]	Donanemab	AD	8[redacted]	[redacted]	[redacted]	Heterozygous	99	None	—	Occipital lobe	—	—	—
	Haemorrhagic stroke	Donanemab	AD	8[redacted]	[redacted]	[redacted]	Heterozygous	203	Aspirin	Moderate	Frontal lobe	Continued	Not resolved	Yes
	Haemorrhagic stroke	Donanemab	MCI	7[redacted]	[redacted]	[redacted]	Heterozygous	402	Nonaspirin antiplatelet	Severe	—	Discontinued	Sequelae	Yes
	Cerebral haemorrhage	Donanemab	MCI	7[redacted]	[redacted]	[redacted]	Heterozygous	74	None	Severe	Occipital lobe	Discontinued	Resolved	No

[a] Used within 30 days prior to the occurrence of the event
[b] Based on MRI
[c] Treatment group in Study AACI (double-blind period)
[d] Number of days after the start of the extension period

Table 61. Outline of the events in the subject who developed cerebral hemorrhage and hemorrhagic stroke on the same day as the onset of serious ARIA-H and died subsequently in Study AACI (double-blind period)

After the start of donanemab treatment[a]	Events
Day 46	The patient developed mild symptomatic ARIA-E. On the same day, mild headache in the right frontal to the temporal region was reported. The study drug treatment was interrupted and was not resumed thereafter.
Day 71	An MRI showed mild ARIA-E and 1 microhemorrhage in the left parietal, right occipital, and right temporal robes, with areas of superficial siderosis in the left frontal (65 mm), right occipital (6 mm), right parietal (4 mm), and right temporal lobes (7 mm).
Day 72	The ARIA-H was reported as serious and severe. On the same day, the patient was hospitalized due to hemiplegia and aphagia with concurrent severe cerebral hemorrhage with mass effect and hemorrhagic stroke. A brain CT scan showed a left parietal hematoma (5.5 cm × 4.3 cm). On the same day, the patient was transferred to the palliative care department due to deterioration in the patient's condition.
Day 75	The patient died. The causes of death were reported as hemorrhagic stroke and ARIA-H. ARIA-E and ARIA-H were considered related to the study drug.

[a] The screening MRI scan showed superficial siderosis (50 mm) in the left frontal lobe.

Some patients were excluded from enrollment in Studies AACG and AACI due to MRI findings. Given the risk of developing ARIA when donanemab is administered to such patients, the following measures should be considered: Donanemab is contraindicated in patients whose baseline MRI shows the presence of vasogenic cerebral edema, ≥5 cerebral microhemorrhages, and cerebral hemorrhage >1 cm, because such patients are at the increased risk of ARIA. Donanemab is contraindicated in patients whose baseline MRI shows the presence of superficial siderosis, regardless of the number of areas of superficial siderosis, for reasons including the following: (1) in the donanemab group in Dona-PC, the incidence of ARIA was higher in subjects whose baseline MRI had shown the presence of 1 area of superficial siderosis compared to those whose baseline MRI

had not; and (2) donanemab will be used in a wider range of patients in the post-marketing setting than was the case in the clinical studies.

In the clinical studies, patients whose baseline MRI had shown the presence of severe white matter disease were excluded to avoid potential confounding effects of non-AD associated causes of memory impairment or cognitive impairment. However, in Dona-PC, the baseline severity of white matter disease did not tend to affect the incidence of ARIA (Table 62) or the severity of first ARIA; therefore, instead of contraindicating the use of donanemab in such patients, it would be more reasonable to include this patient population in the Precautions section for patients with specific characteristics.

Table 62. Incidence of ARIA by the severity of white matter disease in Dona-PC

	Absence of white matter disease	Presence of white matter disease[a]			
		Any severity	Severity grade 1	Severity grade 2	Severity grade 3
Placebo (N = 999)	5.9 (5/85)	14.3 (131/913)	14.1 (116/822)	16.7 (15/90)	0.0 (0/1)
Donanemab (N = 984)	25.5 (24/94)	37.8 (336/890)	37.2 (300/807)	43.4 (36/83)	0.0 (0/0)

% (n/N)

[a] The severity of white matter disease was rated on a scale system and classified into 3 grades: severity grade 1 for focal lesions; severity grade 2 for beginning confluence of lesions; and severity grade 3 for diffuse involvement of the entire region (regardless of involvement of U fibers) (*Stroke.* 2001;32:1318-22). Lesions were assessed by the central read, and the severity of white matter disease were rated in all the cerebral regions (frontal region, parieto-occipital region, temporal region, infratentorial/cerebellum, and basal ganglia) for the right and left hemispheres, and the higher hemisphere score was used.

(b) ARIA monitoring and whether to treat patients with findings of ARIA

The applicant's explanation about the rules for MRI scans required for ARIA monitoring:

To manage ARIA appropriately as an important risk factor in the treatment with donanemab and prevent severe ARIA events, MRI scans should be performed in a timely manner prior to and during treatment with donanemab under the supervision of physicians with knowledge of and experience in the treatment of ARIA to closely monitor and evaluate radiographic findings and the presence of symptoms. Therefore, cautionary statements to this effect will be included in the "Warnings" section of the package insert. The most suitable timing for performing MRI scans during treatment with donanemab will be discussed later.

The applicant's explanation as to whether donanemab can be used in patients with ARIA findings:

In Studies AACG and AACI, MRI scans were performed prior to the administration of study drug at Weeks 4, 12, 16 (Study AACG only), 24, 36 (Study AACG only), and 52. If there were any symptoms suggestive of ARIA after the start of treatment with donanemab, unscheduled MRI was to be performed at the discretion of the investigator, regardless of the number of weeks. If ARIA occurred, donanemab could be continued or resumed after interruption at the discretion of the principal investigator, according to the procesures shown in Tables 24 and 31, or other guidance [see Sections "7.3 Foreign phase II study" and "7.4 Global phase III study"].

In Dona-PC, 56 subjects continued treatment with donanemab after the first onset of ARIA-E. Of the 56 subjects, 10 subjects experienced recurrent ARIA-E events, all of which were mild or moderate in severity on MRI. Of the 10 subjects who experienced recurrent ARIA-E, 2 were symptomatic. The symptoms and

MRI findings were reported as resolved in both subjects. A total of 123 subjects resumed donanemab treatment after dose interruption following the first onset of ARIA-E. Of the 123 subjects, 41 subjects experienced recurrent ARIA-E, 2 of whom had severe ARIA-E on MRI. Of the 41 subjects experiencing recurrent ARIA-E, 13 subjects had symptoms, and 2 of whom had severe ARIA-E on MRI. Both events were considered related to donanemab by the principal investigator, with one subject reported as “recovered” based on MRI findings and the other subject died.

In Dona-PC, there were no marked differences in patient characteristics between subjects whose donanemab doses were interrupted due to ARIA and experienced recurrent ARIA-E after resumption and those who did not experience recurrent ARIA-E (Table 63).

Table 63. Patient characteristics in the subgroup of subjects who experienced recurrent ARIA-E and the subgroups of subjects who did not after resuming donanemab following interruption of donanemab due to onset of ARIA in Dona-PC

	Subjects without recurrent ARIA-E (N = 82)	Subjects with recurrent ARIA-E (N = 41)
ApoE ε4 carrier status		
Homozygous	26.8 (22)	26.8 (11)
Heterozygous	56.1 (46)	53.7 (22)
Non-carrier	17.1 (14)	19.5 (8)
Baseline amyloid PET Centiloid scale		
<50	9.8 (8)	4.9 (2)
≥50 and ≤100	36.6 (30)	34.1 (14)
>100	53.7 (44)	61.0 (25)
Amyloid PET Centiloid scale before resumption of donanemab		
<50	47.6 (39)	31.7 (13)
≥50 and ≤100	26.8 (22)	34.1 (14)
>100	25.6 (21)	34.1 (14)
Number of baseline microhemorrhages		
0	82.9 (68)	85.4 (35)
1	8.5 (7)	9.8 (4)
≥2	8.5 (7)	4.9 (2)
Number of microhemorrhages before resumption of donanemab		
0	42.7 (35)	34.1 (14)
1	12.2 (10)	17.1 (7)
≥2	45.1 (37)	48.8 (20)
Superficial siderosis		
Presence of superficial siderosis at baseline	2.4 (2)	0 (0)
Presence of superficial siderosis before resumption of donanemab	35.4 (29)	22.0 (9)
Severity[a] of white matter disease at baseline		
Presence of lesion in any severity	93.9 (77)	100.0 (41)
Severity grade 1	84.1 (69)	92.7 (38)
Severity grade 2	9.8 (8)	7.3 (3)
Severity grade 3	0 (0)	0 (0)
Severity[a] of white matter disease before resumption of donanemab		
Presence of lesion in any severity	93.9 (77)	100.0 (41)
Severity grade 1	84.1 (69)	92.7 (38)
Severity grade 2	9.8 (8)	7.3 (3)
Severity grade 3	0 (0)	0 (0)

% (n)

[a] The severity of white matter disease was rated on a scale system and classified into 3 grades: severity grade 1 for focal lesions; severity grade 2 for beginning confluence of lesions; and severity grade 3 for diffuse involvement of the entire region (regardless of involvement of U fibers) (*Stroke.* 2001;32:1318-22). Lesions were assessed by the central read, and the severity of white matter disease was rated in all the cerebral regions (frontal region, parieto-occipital region, temporal region, infratentorial/cerebellum, and basal ganglia) for the right and left hemispheres, and the higher hemisphere score was used.

In Dona-PC, 118 subjects continued receiving donanemab after the onset of the first ARIA-H,[37)] among whom 51 subjects experienced recurrent ARIA-H. Of the 51 subjects with recurrent ARIA-H, 21 subjects had severe ARIA-H on MRI, 3 of whom had symptoms. The ARIA-H events in these 3 subjects were considered related to donanemab by the principal investigator. Of the 3 subjects, 2 had stabilized ARIA-H on MRI and 1 did not

37) When ARIA-H is concurrent with ARIA-E, it is difficult to differentiate symptoms for ARIA-H from those of ARIA-E, and therefore, the symptoms associated with symtomatic ARIA-H were not collected in a systematic manner. For this reason, data were analyzed based on events coded to Medical dictionary for regulatory activities (MedDRA) lowest level terms (LLTs) “symptomatic ARIA-H,” “symptomatic ARIA-microhaemorrhages and haemosiderin deposits,” “ARIA-H microhaemorrhage, symptomatic,” and “symptomatic ARIA-superficial siderosis.”

recovered. A total of 81 subjects resumed donanemab treatment after dose interruption following the first onset of ARIA-H. Of the 81 subjects, 42 subjects experienced recurrent ARIA-H, 29 of whom were assessed as severe on MRI. Of the 29 subjects, 2 had symptoms, 1 of whom developed ARIA-H after dose interruption due to the first ARIA-E. This subject resumed donanemab treatment after confirmed resolution of ARIA-E on MRI, and subsequently developed symptomatic ARIA-H. Resolution of symptoms (confusional state) and stabilized ARIA-H on MRI were reported in the subject. The principal investigator assessed ARIA-Eas related to donanemab and ARIA-H as unrelated to donanemab. The other subject was described above as the patient who died after experiencing recurrent ARIA-E. This subject was an *APOE4* heterozygote. Table 64 summarizes the events occurring in this subject. According to the applicant, although this patient had been treated in accordance with the protocol of Study AACI, the patient characteristics and specific circumstances such as willingness to receive treatment could have substantially contributed to the fatal outcome.

Table 64. Outline of events in the subject who died after ARIA recurrence in Study AACI (double-blind period)

After the start of donanemab treatment	Events
Day 79	The patient developed asymptomatic, severe ARIA-E and mild ARIA-H on MRI, and donanemab treatment was interrupted.
Day 167	An MRI showed stabilized ARIA-H.
Day 195	An MRI showed complete resolution of ARIA-E.
Day 202	Donanemab treatment was resumed.
Day 399	Last dose of donanemab
Day 413	Confusional state and balance disorder were reported.
Day 423	An MRI showed ARIA-E and ARIA-H, which were assessed as symptomatic.
Day 427	The patient was admitted to the ICU, and treatment with dexamethasone was initiated.
Day 428	General medical care was stopped, and the patient was discharged to a hospice. Subsequently, the patient was transferred to a skilled nursing facility for palliative care.
Day 447	The patient died. The cause of death is unknown. The investigator assessed the death as related to the study drug.

In Dona-PC, subjects who experienced recurrent ARIA-H after dose resumption following the interruption of donanemab due to ARIA and those who did not were analyzed for their baseline characteristics. The proportion of subjects with the following characteristics tended to be higher in the subgroup of subjects who experienced recurrent ARIA-H than in the subgroup of subjects who did not; however, no factors were identified for recurrence of ARIA after resumption of donanemab.

- Homozygous *APOE4* carriers
- Amyloid PET >100 Centiloids before resumption of donanemab treatment
- ≥2 cerebral microhemorrhages or white matter severity grade 2 at baseline and before the resumption of donanemab treatment

Based on the above discussion and the incidence of the first ARIA in Study AACI (Tables 53 and 54), the risk of ARIA after the start of treatment with donanemab can be managed in an appropriate manner by following the guidance specified in the protocol of Study AACI. The safety in ApoE ε4 carriers can be ensured by advising such patient population of the increased ARIA risk and by monitoring the patient population for ARIA as with the case of non-carrier patients. Based on the guidance specified in the protocol of Study AACI, as well as relevant factors, such as timing at which the first ARIA event commonly occurs and the burden on patients,

caregivers, and medical institutions, periodical MRI scans during treatment with donanemab should be performed prior to the infusion at Weeks 4, 12, and 24, and thereafter to monitor patients for ARIA. In addition, given that many serious events of ARIA occurred within 12 weeks after the start of donanemab treatment (see Table 59), it is advisable to perform an MRI scan prior to the donanemab infusion at Week 8, as necessary. If ARIA has occurred after the start of donanemab treatment, MRI scans should be performed to determine the presence of ARIA. In this case, the timing of MRI scans should vary, as described below, depending on the type and severity of ARIA and whether donanemab treatment is continued. A comprehensive assessment based on the patient's characteristics (e.g., ApoE ε4 carrier status, *APOE4* genotype, cerebral microhemorrhage, superficial siderosis, and white matter disease) and the patient's condition should desirably be performed to determine whether donanemab treatment should be resumed after interruption due to ARIA.

- If donanemab treatment is continued after the onset of radiographically mild, asymptomatic ARIA-E, consider an MRI scan at approximately 1 to 2 months after onset to assess if the severity of ARIA has increased.
- If donanemab treatment is interrupted due to the occurrence of radiographically moderate or severe, or symptomatic ARIA-E, perform an MRI scan at approximately 2 to 4 months after onset, given that the median time from onset to resolution of ARIA-E was approximately 9 weeks in the clinical studies.
- If donanemab treatment is interrupted due to the occurrence of radiographically mild and symptomatic, or radiographically moderate or severe ARIA-H, perform an MRI scan at approximately 2 to 4 months after onset, in accordance with the method for monitoring ARIA-E.

The information on ARIA in clinical studies, such as the method for differential diagnosis of ARIA, guidance on actions to be taken in the event of ARIA, and the incidence of ARIA, will be provided using information materials for healthcare professionals.

(c) Relationship of the risk of ARIA with donanemab and concomitant antithrombotic drugs

The applicant's explanation about the relationship between the risk of ARIA associated with donanemab and concomitant antithrombotic use[38)]:

Table 65 shows the incidence of ARIA and cerebral hemorrhage by concomitant antiplatelet or anticoagulant use in Dona-PC and All-Dona. The incidence of ARIA-E- and ARIA-H-related events by severity in the concomitant antithrombotic use group did not differ markedly from that in the no concomitant antithrombotic use group regardless of the type of antithrombotic agent or radiographic severity. The incidence of cerebral hemorrhage in the concomitant antithrombotic use group did not differ markedly from that in the no concomitant antithrombotic use group.

[38)] Antiplatelet drugs, anticoagulant drugs, and thrombolytic drugs

Table 65. Incidence of ARIA and cerebral hemorrhage by concomitant antiplatelet or anticoagulant use in Dona-PC and All-Dona

	Dona-PC		All-Dona (N = 2727)
	Placebo (N = 999)	Donanemab (N = 984)	
ARIA-E			
Concomitant antithrombotic not used[a]	1.8 (10/569)	25.5 (146/573)	20.3 (320/1578)
Severity on MRI[b]			
Mild	60.0 (6)	26.7 (39)	31.9 (102)
Moderate	40.0 (4)	65.1 (95)	60.6 (194)
Severe	0 (0)	8.2 (12)	7.5 (24)
Concomitant antithrombotic used[d]	1.6 (7/430)	20.7 (85/411)	16.4 (189/1149)
Type of concomitant antithrombotic			
Aspirin	1.8 (6/342)	20.7 (69/333)	17.5 (161/918)
Non-aspirin antiplatelet	0 (0/40)	17.2 (10/58)	10.6 (15/142)
Anticoagulant	1.0 (1/104)	17.3 (17/98)	11.0 (30/272)
Thrombolytic	0 (0/2)	0 (0/1)	0 (0/2)
Severity on MRI[b]			
Mild	85.7 (6)	32.1 (27)	34.6 (65)
Moderate	14.3 (1)	58.3 (49)	54.8 (103)
Severe	0 (0)	9.5 (8)	10.6 (20)
ARIA-H			
Concomitant antithrombotic not used[a]	12.0 (68/569)	30.0 (172/573)	24.5 (387/1578)
Severity on MRI[c]			
Mild	85.3 (58)	47.7 (82)	54.3 (210)
Moderate	13.2 (9)	18.0 (31)	16.5 (64)
Severe	1.5 (1)	34.3 (59)	29.2 (113)
Concomitant antithrombotic used[d]	12.8 (55/430)	29.9 (123/411)	25.1 (288/1149)
Type of concomitant antithrombotic			
Aspirin	13.5 (46/342)	31.2 (104/333)	26.8 (246/918)
Non-aspirin antiplatelet	20.0 (8/40)	24.1 (14/58)	21.8 (31/142)
Anticoagulant	11.5 (12/104)	22.4 (22/98)	17.3 (47/272)
Thrombolytic	0 (0/2)	0 (0/1)	0 (0/2)
Severity on MRI[c]			
Mild	76.4 (42)	47.2 (58)	53.1 (153)
Moderate	14.5 (8)	21.1 (26)	14.2 (41)
Severe	9.1 (5)	31.7 (39)	32.6 (94)
Cerebral hemorrhage			
Concomitant antithrombotic not used[a]	0.4 (2/569)	0.3 (2/573)	0.1 (2/1578)
Concomitant antithrombotic used[d]	0 (0/430)	0.2 (1/411)	0.3 (4/1149)

% (n)

[a] Incidence (%) = (number of subjects who developed events / number of subjects with no concomitant antithrombotic use) × 100

[b] Calculated using the number of ARIA-E events as a denominator.

[c] Calculated using the number of ARIA-H events as a denominator.

[d] Incidence (%) = (number of subjects who developed the event and had used an antithrombotic within 30 days prior to the onset of the event / number of subjects who had taken at least one dose of an antithrombotic) × 100

The above results suggest no clear increased risk of ARIA or cerebral hemorrhage associated with the use of concomitant antithrombotics. A cautionary statement regarding the potential onset of ARIA-H or cerebral hemorrhage associated the use of concomitant antithrombotic will be included in the “Precautions Concerning Coadministration” section of the package insert.

PMDA's view regarding Subsections (a), (b), and (c) above:
Based on the clinical study results presented, donanemab should be contraindicated in patients with findings showing the presence of vasogenic cerebral edema, ≥5 cerebral microhemorrhages, and cerebral hemorrhage >1 cm, and patients with findings showing the presence of superficial siderosis before the start of treatment with donanemab. It is acceptable not to contraindicate the use of donanemab in patients with baseline findings showing severe white matter disease, provided that the package insert appropriately include a cautionary statement to the effect that donanemab has never been used in such patients. The applicant presented cautionary statements regarding patient monitoring to reduce the risk and actions to be taken in the event of ARIA, which are considered appropriate. Additionally, to manage the risk of ARIA, donanemab must be used under the supervision of physicians with adequate knowledge of and experience in the treatment of ARIA, and physicians must have the skills that allow them to read brain MRI scans properly so that an accurate diagnosis of ARIA can be made; therefore, physicians are required to attend a training program for healthcare professionals on MRI assessment of ARIA before using donanemab.

The appropriateness of the decision above and detailed cautionary statements regarding ARIA will be finalized taking into account the comments from the Expert Discussion. Whether donanemab can be used concomitantly with antithrombotics will be discussed later, taking into account the results of discussions in Section "7.R.4.2 Hemorrhage-related events in the central nervous system."

7.R.4.2 Hemorrhage-related events in the central nervous system

The applicant's explanation about the relationship between donanemab and CNS hemorrhage-related events:
Table 66 shows the incidence of CNS hemorrhage-related events[39)] in Dona-PC and All-Dona, and Table 67 shows the list of subjects[40)] who developed CNS hemorrhage-related events[39)] other than microhemorrhage in Study AACG, Study AACH Part B, Study AACI (double-blind period), Study AACI (extension period), and Study AACI Addendum 9. There were no CNS hemorrhage-related events[39)] occurring at an incidence higher than that of cerebral microhemorrhage, a known risk for donanemab, in Dona-PC or All-Dona.

[39)] Events coded to Standardised MedDRA queries (SMQ) "haemorrhagic central nervous system vascular conditions" (20000064).
[40)] Excluding subjects with cerebral hemorrhage listed in Table 60.

Table 66. Incidence of CNS hemorrhage-related events[39)] in Dona-PC and All-Dona

	Dona-PC		All-Dona
	Placebo (N = 999)	Donanemab (N = 984)	Donanemab (N = 2727)
Haemorrhagic central nervous system vascular conditions (SMQ)	2.2 (22)	4.7 (46)	3.6 (99)
Cerebral microhaemorrhage	1.5 (15)	2.8 (28)	2.1 (58)
Subdural haematoma	0.1 (1)	0.5 (5)	0.4 (11)
Cerebellar microhaemorrhage	0 (0)	0.4 (4)	0.2 (6)
Cerebrovascular accident	0.1 (1)	0.3 (3)	0.3 (7)
Cerebral haemorrhage	0.1 (1)	0.2 (2)	0.1 (4)
Subarachnoid haemorrhage	0.1 (1)	0.2 (2)	0.2 (5)
Brain stem microhaemorrhage	0 (0)	0.1 (1)	0 (1)
Extradural haematoma	0 (0)	0.1 (1)	0 (1)
Haemorrhagic stroke	0.1 (1)	0.1 (1)	0.1 (3)
Cerebral haematoma	0.1 (1)	0 (0)	0.1 (2)
Intraventricular haemorrhage	0.1 (1)	0 (0)	0 (0)
Spinal epidural haematoma	0.1 (1)	0 (0)	0 (0)
Haemorrhage intracranial	0 (0)	0 (0)	0 (1)
Subdural haemorrhage	0 (0)	0 (0)	0 (1)
Thalamus haemorrhage	0 (0)	0 (0)	0 (1)
Serious events	0.3 (3)	0.9 (9)	0.7 (18)
Events leading to death	0 (0)	0.1 (1)	0.1 (2)

% (n)

Table 67. List of donanemab-treated subjects[40] who developed CNS hemorrhage-related events[39] other than microhemorrhage in Study AACG, Study AACH Part B, Study AACI (double-blind period), Study AACI (extension period), and Study AACI Addendum 9 (safety analysis set)

Study	PT	Treatment group	MCI /AD	Age (years)	Sex	Race	ApoE ε4 carrier status	Onset (Day)	Concomitant antithrombotic use[a]	Severity	Donanemab disposition	Clinical outcome of hemorrhage	Related
AACG	Extradural haematoma	Donanemab	MCI	8[redacted]	[redacted]	[redacted]	Non-carrier	416	Aspirin	Severe	Continued	Resolved	No
	Subdural haematoma							416	Aspirin	Severe	Continued	Resolved	No
	Cerebrovascular accident	Donanemab	AD	8[redacted]	[redacted]	[redacted]	Non-carrier	113	Aspirin	Moderate	Continued	Resolved	No
AACH Part B	Subarachnoid haemorrhage	Placebo[b]	AD	8[redacted]	[redacted]	[redacted]	Non-carrier	177	None	Moderate	Discontinued	Not resolved	Yes
AACI (double-blind)	Subarachnoid haemorrhage	Donanemab	AD	7[redacted]	[redacted]	[redacted]	Homozygous	152	Aspirin	Severe	Interrupted	Resolved	No
	Subarachnoid haemorrhage							176	Aspirin	Severe	Continued	Resolved	No
	Subdural haematoma	Donanemab	AD	8[redacted]	[redacted]	[redacted]	Heterozygous	71	Aspirin	Moderate	Interrupted	Resolved	No
	Subarachnoid haemorrhage	Donanemab	AD	8[redacted]	[redacted]	[redacted]	Non-carrier	237	Aspirin	Severe	Discontinued	Death	No
	Subdural haematoma	Donanemab	AD	8[redacted]	[redacted]	[redacted]	Non-carrier	365	None	Mild	Interrupted	Resolving	No
	Subdural haematoma							442	None	Mild	Continued	Resolved	No
	Subdural haematoma							443	None	Mild	Interrupted	Resolving	Yes
	Cerebrovascular accident	Donanemab	AD	7[redacted]	[redacted]	[redacted]	Non-carrier	466	Aspirin and non-aspirin antiplatelet	Severe	Continued	Not resolved	No
	Subdural haematoma	Donanemab	AD	7[redacted]	[redacted]	[redacted]	Non-carrier	429	None	Moderate	Continued	Not resolved	No
	Subdural haematoma	Donanemab	AD	8[redacted]	[redacted]	[redacted]	Non-carrier	86	None	Severe	Discontinued	Resolved	No
	Cerebrovascular accident	Donanemab	AD	6[redacted]	[redacted]	[redacted]	Heterozygous	148	None	Moderate	Continued	Not resolved	No
AACI (extension)	Haemorrhage intracranial	Placebo[b]	AD	7[redacted]	[redacted]	[redacted]	Heterozygous	137[c]	Thrombolytic	Severe	Continued	Unknown[d]	No
	Subdural haematoma	Placebo[b]	MCI	6[redacted]	[redacted]	[redacted]	Heterozygous	86[c]	None	Mild	Continued	Not resolved	No
	Subarachnoid haemorrhage	Placebo[b]	AD	6[redacted]	[redacted]	[redacted]	Homozygous	99[c]	Aspirin	Severe	Discontinued	Resolving	No
	Subdural haematoma	Placebo[b]	MCI	6[redacted]	[redacted]	[redacted]	Heterozygous	71[c]	Aspirin	Moderate	Interrupted	Resolved	No
	Subdural haematoma							106[c]	None	Moderate	Continued	Resolved	No
	Cerebrovascular accident	Placebo[b]	AD	7[redacted]	[redacted]	[redacted]	Heterozygous	128[c]	Aspirin	Severe	Continued	Not resolved	Yes
AACI Addendum 9	Thalamus haemorrhage	Donanemab	MCI	7[redacted]	[redacted]	[redacted]	Heterozygous	409	None	Severe	Continued	Death	Yes
	Cerebrovascular accident	Donanemab	MCI	7[redacted]	[redacted]	[redacted]	Non-carrier	220	Aspirin	Severe	Continued	Resolved	No
	Subdural haemorrhage	Donanemab	AD	6[redacted]	[redacted]	[redacted]	Non-carrier	14	None	Mild	Continued	Resolved	No
	Subarachnoid haemorrhage							17	None	Mild	Interrupted	Resolved	No
	Subdural haematoma	Donanemab	MCI	7[redacted]	[redacted]	[redacted]	Heterozygous	99	Aspirin	Moderate	Interrupted	Not resolved	No
	Cerebral haematoma	Donanemab	MCI	6[redacted]	[redacted]	[redacted]	Heterozygous	133	None	Mild	Continued	Resolved	No
	Subdural haematoma	Donanemab	AD	7[redacted]	[redacted]	[redacted]	Non-carrier	33	None	Mild	Interrupted	Resolved	No
	Cerebrovascular accident	Donanemab	MCI	7[redacted]	[redacted]	[redacted]	Heterozygous	22	Aspirin	Mild	Interrupted	Resolved	No
	Subdural haematoma	Donanemab	AD	6[redacted]	[redacted]	[redacted]	Heterozygous	114	None	Severe	Continued	Resolved	No
	Subdural haematoma	Donanemab	AD	7[redacted]	[redacted]	[redacted]	Non-carrier	89	Non-aspirin antiplatelet	Mild	Interrupted	Not resolved	No
	Cerebrovascular accident	Donanemab	AD	7[redacted]	[redacted]	[redacted]	Heterozygous	112	None	Moderate	Interrupted	Not resolved	No

Study	PT	Treatment group	MCI /AD	Age (years)	Sex	Race	ApoE ε4 carrier status	Onset (Day)	Concomitant antithrombotic use[a]	Severity	Donanemab disposition	Clinical outcome of hemorrhage	Related
	Cerebral haematoma	Donanemab	AD	6[redacted]	[redacted]	[redacted]	Heterozygous	93	None	Mild	Continued	Resolved	No

[a] Used within 30 days prior to the occurrence of the event
[b] Treatment group in Study AACG or Study AACI (double-blind period)
[c] Number of days after the start of the extension period
[d] After a thrombolytic was administered for the treatment of ischaemic stroke, which occurred on the same day as haemorrhage intracranial, the patient developed multiple hemorrhages. Subsequently, the patient died.

Table 68 shows the incidence of CNS hemorrhage-related events[39)] by concomitant antithrombotic use in Dona-PC and All-Dona. In both Dona-PC and All-Dona, the incidence of CNS hemorrhage-related events[39)] was higher in the concomitant antithrombotic use group than in the no concomitant antithrombotic use group, although the incidence of the events in the donanemab group increased to a similar extent to that in the placebo group. Based on this and other factors, the risk of concomitant antithrombotic use does not exceed the known risk associated with antithrombotic use.

Table 68. Incidence of CNS hemorrhage-related events[39)] by concomitant antithrombotic use in Dona-PC and All-Dona

	Dona-PC				All-Dona	
	Concomitant antithrombotic used[a]		No concomitant antithrombotic used[b]		Concomitant antithrombotic used[a]	No concomitant antithrombotic used[b]
	Placebo (N = 430)	Donanemab (N = 411)	Placebo (N = 569)	Donanemab (N = 573)	Donanemab (N = 1149)	Donanemab (N = 1578)
Haemorrhagic central nervous system vascular conditions (SMQ)	2.8 (12)	6.3 (26)	1.6 (9)	3.1 (18)	4.6 (53)	2.5 (40)
Cerebral microhaemorrhage	1.9 (8)	3.9 (16)	1.1 (6)	1.9 (11)	2.9 (33)	1.3 (21)
Subdural haematoma	0 (0)	0.5 (2)	0.2 (1)	0.5 (3)	0.4 (5)	0.4 (6)
Cerebellar microhaemorrhage	0 (0)	0.5 (2)	0 (0)	0.3 (2)	0.2 (2)	0.3 (4)
Cerebrovascular accident	0.2 (1)	0.5 (2)	0 (0)	0 (0)	0.4 (5)	0.1 (1)
Cerebral haemorrhage	0 (0)	0.2 (1)	0.2 (1)	0.2 (1)	0.1 (1)	0.1 (2)
Subarachnoid haemorrhage	0.2 (1)	0.5 (2)	0 (0)	0 (0)	0.3 (3)	0.1 (2)
Haemorrhagic stroke	0 (0)	0 (0)	0.2 (1)	0.2 (1)	0.2 (2)	0.1 (1)
Brain stem microhaemorrhage	0 (0)	0.2 (1)	0 (0)	0 (0)	0.1 (1)	0 (0)
Cerebral haematoma	0.2 (1)	0 (0)	0 (0)	0 (0)	0 (0)	0.1 (2)
Extradural haematoma	0 (0)	0.2 (1)	0 (0)	0 (0)	0.1 (1)	0 (0)
Intraventricular haemorrhage	0.2 (1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Spinal epidural haematoma	0 (0)	0 (0)	0.2 (1)	0 (0)	0 (0)	0 (0)
Haemorrhage intracranial	0 (0)	0 (0)	0 (0)	0 (0)	0.1 (1)	0 (0)
Subdural haemorrhage	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0.1 (1)
Thalamus haemorrhage	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0.1 (1)
Serious events	0.5 (2)	1.5 (6)	0.2 (1)	0.5 (3)	1.0 (11)	0.4 (6)
Events leading to death	0 (0)	0.2 (1)	0 (0)	0 (0)	0.1 (1)	0.1 (1)

% (n)
[a] Incidence (%) = (number of subjects who developed the event and had used an antithrombotic within 30 days prior to the onset of the event / number of subjects who had used at least one dose of an antithrombotic) × 100
[b] Incidence (%) = (number of subjects who developed events / number of subjects with no concomitant antithrombotic use) × 100

During the extension period of Study AACI, 1 subject was transported to an emergency outpatient department, where a thrombolytic agent was used to treat acute ischemic stroke, after which the subject developed multiple hemorrhages, and subsequently died (Table 67). Stroke was not considered related to the study drug by the investigator. However, tenecteplase-induced bleeding may have been further exacerbated by cerebral amyloid angiopathy and the amyloid removal effect of the blinded study drug.

In an ongoing foreign study (Study AACQ[41)]), 1 subject developed intracranial hemorrhage after administration of a thrombolytic agent (recombinant tissue-type plasminogen activator [rt-PA]) (Table 69). The applicant sent a letter to the medical institutions participating in the clinical study to ensure again that healthcare professionals are made aware of the potential risk of cerebral hemorrhage caused by thrombolytic use in patients treated with donanemab.

Table 69. Outline of events in the subject who developed intracranial hemorrhage after receiving thrombolytic agent in Study AACQ

After the last dose of donanemab	Events
9 days	MRI findings showed the presence of asymptomatic, mild ARIA-E (<5 cm, one side, right parietal region), and mild and asymptomatic ARIA-H (6 microhemorrhages in the right parietal region, not greater than 10 mm, no cerebral hemosiderin deposits).
16 days	The patient was diagnosed as having middle cerebral artery stroke. Tenecteplase (unknown dosage) was administered intravenously.
17 days	Intracranial hemorrhage occurred.
18 days	The patient died. The causes of death were reported as intraparenchymal haemorrhage in the right cerebrum accompanied by midline shift, acute respiratory failure due to terminal extubation, thrombolytic use for treating cerebral infarction, and possibility of an adverse reaction to the Alzheimer's disease study drug. While middle cerebral artery stroke was considered related to the unblinded study drug by the principal investigator, intracranial hemorrhage was assessed as unrelated to the blinded study drug.

In clinical settings, anticoagulant, antiplatelet, or thrombolytic treatment may become necessary in a healthcare facility different from the hospital where the patient is receiving donanemab. In this case, it must be ensured that healthcare professionals are made aware that the patient has been treated with donanemab and that special precautions are required when such medications are coadministered with donanemab. The applicant, therefore, will take measures such as the use of a patient's medical information card carried by the patient.

Table 70 shows the incidence of ARIA-H[42)] or CNS hemorrhage-related events[39)] in Dona-PC and All-Dona by risk factor for cerebral hemorrhage (*Japan Stroke Society Guidelines 2021 for the treatment of stroke.* Revised version 2023 [in Japanese] Kyowa Kikaku; 2023, *N Engl J Med.* 2022;387:1589-96). Given that the effects of the assessed risk factors in the donanemab group were almost similar to those in the placebo group, donanemab is unlikely to increase the risk of CNS hemorrhage-related events, including ARIA-H, in patients with these risk factors.

41) An ongoing foreign phase III study conducted to investigate how different donanemab dosage regimens affect the incidence of ARIA-E in patients with early AD
42) Based on MRI or TEAE cluster

Table 70. Incidence of ARIA-H[42)] or CNS hemorrhage-related events[39)] by risk factor for cerebral hemorrhage in Dona-PC and All-Dona

Risk factor	Category	Dona-PC		All-Dona
		Placebo (N = 999)	Donanemab (N = 984)	Donanemab (N = 2727)
Age	<65 years	6.6 (6/91)	28.0 (26/93)	22.9 (44/192)
	≥65 years and <75 years	13.4 (60/448)	31.3 (147/469)	26.8 (311/1161)
	≥75 years and <85 years	14.0 (62/444)	33.3 (134/402)	26.1 (337/1291)
	≥85 years	37.5 (6/16)	45.0 (9/20)	30.1 (25/83)
BMI	<25	13.1 (61/465)	33.0 (147/445)	27.4 (318/1159)
	≥25	13.7 (73/534)	31.4 (169/539)	25.4 (398/1566)
Smoking	Current smoker	11.1 (5/45)	27.7 (13/47)	22.3 (31/139)
	Former smoker	14.6 (57/390)	29.4 (113/384)	26.4 (270/1022)
	Never smoker	12.8 (72/564)	34.4 (190/553)	26.8 (400/1495)
Alcohol consumption	Current	13.3 (87/655)	29.7 (188/633)	25.0 (434/1733)
	Former	17.8 (21/118)	35.6 (42/118)	30.9 (93/301)
	Never	11.5 (26/226)	36.9 (86/233)	28.0 (174/622)
Hypertension	Yes	16.4 (91/556)	31.5 (171/542)	26.2 (411/1567)
	No	9.7 (43/443)	32.8 (145/442)	26.4 (306/1160)
Hyperlipidaemia	Yes	13.3 (84/633)	32.9 (208/633)	27.0 (493/1828)
	No	13.7 (50/366)	30.8 (108/351)	24.9 (224/899)
Diabetes mellitus	Yes	14.6 (26/178)	27.4 (45/164)	23.1 (128/554)
	No	13.2 (108/821)	33.0 (271/820)	27.1 (589/2173)
Ischaemic stroke	Yes	25.0 (19/76)	30.3 (27/89)	25.7 (69/268)
	No	12.5 (115/923)	32.3 (289/895)	26.4 (648/2459)
Chronic kidney disease	Yes	23.1 (12/52)	29.4 (15/51)	26.5 (45/170)
	No	12.9 (122/947)	32.3 (301/933)	26.3 (672/2557)
Myocardial infarction	Yes	16.7 (22/132)	33.3 (43/129)	26.3 (102/388)
	No	12.9 (112/867)	31.9 (273/855)	26.3 (615/2339)

% (number of subjects with event / number of subjects in the analysis set)

Table 71 shows the incidence of ARIA-H[42)] or CNS hemorrhage-related events[39)] by race (Asian or non-Asian) in Dona-PC and All Dona. With the exception of amyloid related imaging abnormality-microhaemorrhages and haemosiderin deposits, the incidence of each event was similar between Asian and non-Asian populations. In Dona-PC, the incidence of amyloid related imaging abnormality-microhaemorrhages and haemosiderin deposits was higher in the Asian population than in the non-Asian population; however, in All-Dona, which has a larger sample size, the incidence in the Asian population was similar to that in the non-Asian population. Based on the above, the risk of CNS hemorrhage-related events, including ARIA-H, associated with the use of donanemab in the Asian population (including Japanese) is thought to be comparable to that in the non-Asian population.

Table 71. Incidence of ARIA-H[42)] or CNS hemorrhage-related events[39)] by race in Dona-PC and All-Dona

	Dona-PC				All Dona	
	Asian		Non-Asian		Asian	Non-Asian
	Placebo (N = 49)	Donanemab (N = 58)	Placebo (N = 950)	Donanemab (N = 926)	Donanemab (N = 156)	Donanemab (N = 2571)
ARIA-H or haemorrhagic central nervous system vascular conditions (SMQ)	10.2 (5)	36.2 (21)	13.6 (129)	31.9 (295)	25.6 (40)	26.3 (677)
Amyloid related imaging abnormality-microhaemorrhages and haemosiderin deposits	6.1 (3)	25.9 (15)	6.9 (66)	17.7 (164)	17.3 (27)	15.7 (404)
Superficial siderosis of central nervous system	0 (0)	3.4 (2)	1.5 (14)	8.0 (74)	3.2 (5)	5.6 (144)
Cerebral microhaemorrhage	0 (0)	0 (0)	1.6 (15)	3.0 (28)	0 (0)	2.3 (58)
Subdural haematoma	0 (0)	0 (0)	0.1 (1)	0.5 (5)	0 (0)	0.4 (11)
Cerebrovascular accident	0 (0)	1.7 (1)	0.1 (1)	0.2 (2)	0.6 (1)	0.2 (6)
Cerebellar microhaemorrhage	0 (0)	0 (0)	0 (0)	0.4 (4)	0 (0)	0.2 (6)
Subarachnoid haemorrhage	0 (0)	0 (0)	0.1 (1)	0.2 (2)	0 (0)	0.2 (5)
Cerebral haemorrhage	0 (0)	0 (0)	0.1 (1)	0.2 (2)	0 (0)	0.2 (4)
Haemorrhagic stroke	0 (0)	0 (0)	0.1 (1)	0.1 (1)	0 (0)	0.1 (3)
Cerebral haematoma	0 (0)	0 (0)	0.1 (1)	0 (0)	0 (0)	0.1 (2)
Brain stem microhaemorrhage	0 (0)	0 (0)	0 (0)	0.1 (1)	0 (0)	0 (1)
Extradural haematoma	0 (0)	0 (0)	0 (0)	0.1 (1)	0 (0)	0 (1)
Haemorrhage intracranial	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (1)
Subdural haemorrhage	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (1)
Thalamus haemorrhage	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (1)
Intraventricular haemorrhage	0 (0)	0 (0)	0.1 (1)	0 (0)	0 (0)	0 (0)
Spinal epidural haematoma	0 (0)	0 (0)	0.1 (1)	0 (0)	0 (0)	0 (0)

% (n)

PMDA's view:

The results of donanemab clinical studies indicate that donanemab is unlikely to increase the risk of CNS hemorrhage-related events other than microhemorrhage. The results of subgroup analyses indicate that the risk of ARIA-H or CNS hemorrhage-related events associated with the use of donanemab is likely to similar regardless of risk factors for cerebral hemorrhage, such as elevated blood pressure, or regardless of races.

When any concomitant antithrombotic is used in patients treated with donanemab, such patients should be monitored closely for cerebral hemorrhage considering the factors shown below; however, no clinically unacceptable risks have been identified at present. The following applicant's plans are appropriate: antithrombotic drugs should be listed in the "Precautions Concerning Coadministration" section of the package insert to raise awareness; in addition, if anticoagulant, antiplatelet, or thrombolytic treatment becomes necessary in a healthcare facility different from the hospital where the patient is receiving donanemab, measures should be taken to ensure that healthcare professionals is made aware that the patient has been treated with donanemab and that special cautions are required when such medications are coadministered with donanemab. However, the applicant should provide information in an appropriate manner through information materials to inform healthcare professionals that the patient who had received an antithrombotic concomitantly with donanemab and subsequently died.

- The incidence of CNS hemorrhage-related events[39)] in the clinical studies of donanemab tended to be higher in subjects with concomitant antithrombotic use than in subjects without concomitant antithrombotic use.

- One subject had received a thrombolytic agent during treatment with donanemab in Study AACI (extension period) and developed cerebral hemorrhage, which resulted in death. The possibility of a causal relationship between cerebral hemorrhage and donanemab cannot be completely ruled out in this subject.

The appropriateness of the decision above will be finalized taking into account the comments from the Expert Discussion.

7.R.4.3 Hypersensitivity, anaphylactic reaction, and infusion related reaction

The applicant's explanation about hypersensitivity, anaphylactic reaction, and infusion related reaction:

Among hypersensitivity events[43] reported in Dona-PC, the incidence of hypersensitivity, anaphylactic reaction, and infusion related reaction[44] is shown in Table 72. While the incidences of all the events were higher in the donanemab group than in the placebo group, the outcome of all these events were reported as resolved.

Table 72. Incidence of hypersensitivity, anaphylactic reaction, and infusion related reaction[44] in Dona-PC

	Dona-PC	
	Placebo (N = 999)	Donanemab (N = 984)
Hypersensitivity	0.3 (3)	1.0 (10)
Serious events	0 (0)	0 (0)
Treatment discontinuation	0 (0)	0.4 (4)
Death	0 (0)	0 (0)
Anaphylactic reaction	0 (0)	0.3 (3)
Serious events	0 (0)	0 (0)
Treatment discontinuation	0 (0)	0.3 (3)
Death	0 (0)	0 (0)
Infusion related reaction	0.4 (4)	8.5 (84)
Serious events	0 (0)	0.3 (3)
Treatment discontinuation	0 (0)	3.9 (38)
Death	0 (0)	0 (0)

% (n)

The incidence of immediate[45] hypersensitivity[43] in Dona-PC was higher in the donanemab group (10.2%) than in the placebo group (1.0%), while the incidence of delayed[46] hypersensitivity in the donanemab group (5.2%) was similar to that in the placebo group (5.2%). The incidence of immediate hypersensitivity in All-Dona was 9.0% (246 of 2,727 subjects). In All-Dona, 87.8% of the subjects with infusion-related reaction (IRR) events[47] experienced the events during or within 30 minutes of the administration of the study drug. Both in Dona-PC and in All-Dona, the majority of immediate hypersensitivity events resolved within 24 hours.

Table 73 shows the incidence of immediate[45] hypersensitivity, anaphylactic reaction, and infusion related reaction[44] by severity in All-Dona. Most of these events were mild or moderate in severity.

[43] Events coded to anaphylactic reaction SMQ (narrow), hypersensitivity SMQ (narrow), or angioedema SMQ (narrow)
[44] MedDRA preferred terms (PTs) "infusion related reaction," "anaphylactic reaction," and "hypersensitivity"
[45] Events occurring on the day of study treatment, which were reported on an AE form, or events occurring within 24 hours after study treatment, which were reported on a hypersensitivity follow-up form.
[46] Events occurring before the next study treatment, which did not meet the definition of immediate hypersensitivity.
[47] Events reported on a hypersensitivity follow-up form

Table 73. Incidence of immediate[45)] hypersensitivity, anaphylactic reaction, and infusion related reaction[44)] by severity in All-Dona

		All-Dona
		Donanemab (N = 2727)
Hypersensitivity of any grade		0.6 (15)
Severity	Mild	33.3 (5)
	Moderate	46.7 (7)
	Severe	20.0 (3)
Anaphylactic reaction of any grade		0.3 (8)
Severity	Mild	37.5 (3)
	Moderate	50.0 (4)
	Severe	12.5 (1)
Infusion related reaction of any grade		7.9 (216)
Severity	Mild	56.5 (122)
	Moderate	38.4 (83)
	Severe	5.1 (11)

% (n)

In All-Dona, 164 subjects received donanemab after developing immediate[45)] IRR events[48)] associated with donanemab treatment, and among these 164 subjects, the recurrence rate of IRR events with and without prophylaxis medications for rechallenge was 39.5% (15 of 38 subjects) and 42.1% (53 of 126 subjects), respectively. Among the 164 subjects, the recurrence rate of IRR events with and without slowed infusion rate[49)] for rechallenge was 41.7% (30 of 72 subjects) and 41.3% (38 of 92 subjects), respectively. The results suggest that the recurrence risk of IRR events associated with donanemab treatment is not reduced by prophylacxis medications or slowed infusion rate.

Based on the above results and given the possibility that hypersensitivity, anaphylactic reaction, and infusion related reaction may lead to fatal outcomes, these events will be specified as important identified risks. In addition, cautionary statements on these events will be included in the “Important Precautions” section and “Clinically significant adverse reactions” section of the package insert. Information on these events will be provided using materials for healthcare professionals and materials for patients.

PMDA’s view:

In the clinical studies of donanemab, the incidence of hypersensitivity, anaphylactic reaction, and infusion related reaction,[44)] is higher in the donanemab group than in the placebo group, and serious adverse events were also reported. At present, no effective measures to reduce IRR events[48)] can be presented; however, these adverse events associated with donanemab treatment are manageable by appropriately advising healthcare professionals on the risk of the events, because (1) all these adverse events resolved without special medical care and (2) most of the events of immediate hypersensitivity, anaphylactic reaction, and infusion related reaction were mild or moderate in severity and resolved within 24 hours. Therefore, the applicant’s plans are appropriate, namely, to specify hypersensitivity, anaphylactic reaction, and infusion related reaction as

[48)] Events reported on a hypersensitivity follow-up form or events reported on an AE form, which were also coded to anaphylactic reaction SMQ (narrow), hypersensitivity SMQ (narrow), or angioedema SMQ (narrow)

[49)] Defined as an infusion of donanemab over ≥45 minutes

important identified risks; and to advise healthcare professionals by including cautionary statements regarding these events in the package insert and information materials.

7.R.4.4 Nervous system disorders (e.g., headache)

The applicant's explanation about nervous system disorders (e.g., headache):

Table 74 shows the incidence of nervous system-related adverse events[50)] in Dona-PC and All-Dona. Except for ARIA and headache, the incidence of nervous system-related adverse events in the donanemab group was similar to that in the placebo group in Dona-PC. Based on the above results, and given that cautionary statements regarding ARIA will be included separately in the labeling, headache should be included in the "Other adverse reactions" section of the package insert. Nervous system-related adverse events that may arise associated with ARIA will be included as ARIA-related symptoms in the "Clinically significant adverse reactions" section of the package insert to increase vigilance.

Table 74. Incidence of nervous system-related events[50)] in Dona-PC and All-Dona

	Dona-PC		All-Dona
	Placebo (N = 999)	Donanemab (N = 984)	Donanemab (N = 2727)
Nervous system-related events	34.9 (349)	53.4 (525)	44.7 (1218)
Common events[a]			
Amyloid related imaging abnormality-oedema/effusion	1.8 (18)	24.4 (240)	19.5 (531)
Amyloid related imaging abnormality-microhaemorrhages and haemosiderin deposits	6.9 (69)	18.2 (179)	15.8 (431)
Headache	10.1 (101)	13.1 (129)	10.8 (294)
Superficial siderosis of central nervous system	1.4 (14)	7.7 (76)	5.5 (149)
Dizziness	6.3 (63)	6.5 (64)	5.2 (143)
Syncope	2.9 (29)	3.0 (30)	2.5 (67)
Cerebral microhaemorrhage	1.5 (15)	2.8 (28)	2.1 (58)
Serious events	2.9 (29)	4.6 (45)	4.0 (109)
Events leading to treatment discontinuation	1.1 (11)	6.2 (61)	3.9 (106)

% (n)

[a] Events occurring in ≥2% of subjects in the donanemab group in Dona-PC

PMDA's view:

Some nervous system-related adverse events may occur as symptoms associated with ARIA. The presence of such symptoms offers important information for early detection of and response to ARIA; therefore, the applicant's plan is appropriate.

7.R.4.5 Psychiatric disorders (including suicidal behavior and suicidal ideation)

The applicant's explanation about psychiatric disorders (including suicidal behavior and suicidal ideation):

Table 75 shows psychiatric disorder-related adverse events[51)] noted in Dona-PC and All-Dona. In Dona-PC, the incidence of each event in the donanemab group was similar to that in the placebo group.

[50)] Adverse events coded to MedDRA System organ class (SOC) "nervous system disorders"

[51)] Adverse events coded to MedDRA SOC "psychiatric disorders"

Table 75. Incidence of psychiatric disorder-related events[51)] in Dona-PC and All-Dona

	Dona-PC		All-Dona
	Placebo (N = 999)	Donanemab (N = 984)	Donanemab (N = 2727)
Psychiatric disorder-related events	21.3 (213)	19.0 (187)	13.4 (366)
Common events[a]			
Anxiety	4.3 (43)	4.3 (42)	2.9 (80)
Depression	3.7 (37)	4.0 (39)	2.4 (66)
Confusional state	2.5 (25)	2.3 (23)	1.7 (46)
Insomnia	1.5 (15)	2.3 (23)	1.7 (46)
Serious events	1.7 (17)	1.3 (13)	0.9 (24)
Events leading to treatment discontinuation	0.5 (5)	0.7 (7)	0.3 (9)

% (n)

[a] Events occurring in ≥2% of subjects in the donanemab group in Dona-PC

In Dona-PC, the proportion of subjects who met any of the 5 suicidal ideation categories (1 to 5) in the Columbia Suicide Severity Rating Scale (C-SSRS) was 3.9% (38 of 978 subjects) in the donanemab group, which is similar to that in the placebo group, 4.5% (45 of 990 subjects). During the double-blind period of Study AACI, suicidal ideation and suicidal behavior, both classified as serious adverse events, occurred in 4 subjects and 2 subjects in the donanemab and placebo groups, respectively. Of the 6 subjects in total, 3 subjects (2 subjects in the donanemab group and 1 subject in the placebo group) died. All the deaths were considered unrelated to the study drug by the investigator.

These results indicated no increased risk of suicidal ideation or suicidal behavior associated with donanemab, and therefore no specific cautionary statements are necessary for psychiatric disorder-related adverse events.

PMDA's view:

No specific concerns have been raised regarding psychiatric disorders such as suicidal behavior and suicidal ideation associated with donanemab. However, as with the case of the nervous system-related adverse events described in Section 7.R.4.4, psychiatric disorder-related adverse events such as confusional state may emerge as ARIA-associated symptoms. Therefore, these symptoms should be identified as ARIA-related symptoms and included in the "Clinically significant adverse reactions" section of the package insert.

7.R.5 Intended patient population and indication of donanemab

The applicant's explanation about the intended patient population of donanemab:

Donanemab acts by removing brain Aβ plaques in patients with AD; therefore, to identify the intended patient population for use of donanemab, brain Aβ pathology needs to be determined. Brain Aβ pathology was assessed by amyloid PET at the time of enrollment of subjects in Study AACI, and the guidelines states that CSF Aβ levels are also highly correlated with brain Aβ pathology as measured by amyloid PET and biopsy (*Clinical Guidelines on the Proper Use of Cerebrospinal Fluid and Blood Biomarkers for Dementia, and APOE Testing.* [in Japanese] Committee for Preparation of the "Clinical Guidelines on the Proper Use of Cerebrospinal Fluid and Blood Biomarkers for Dementia, and APOE Testing";2023:p.6-7). Therefore, prior to the initiation of donanemab treatment, brain Aβ pathology should be assessed using amyloid PET scans, CSF testing, or other testing methods whose results show an established correlation with amyloid pathology.

The criteria for brain tau levels in Study AACI were established to identify patients whose condition was expected to progress during the 76-week evaluation period in order to evaluate the efficacy of donanemab during this period. In Study AACI, according to the inclusion criteria[24)] regarding tau PET, even patients with tau PET SUVr <1.10 could be eligible for the study if there was a deposition pattern consistent with advanced, severe AD by visual read [see Section "7.4 Global phase III study"]. As a result, approximately 15% of randomized subjects had tau PET SUVr <1.10 at screening. As shown in Figure 5, while clinical decline was relatively gradual with a smaller difference from placebo in the tau PET SUVr <1.10 population than in the combined tau PET population, clinical decline on change from baseline in iADRS and that in CDR-SB tended to be slowed in the donanemab group compared to the placebo group. To describe the relationship between AD pathology biomarkers and change in cognition over time, a model has been proposed in which brain Aβ deposition occurs first, and then tau pathology, followed by progression of clinical symptoms (*Lancet Neurol.* 2013;12:207-16). This model suggests that in patients with brain Aβ pathology and insufficient brain tau, clinical decline is relatively gradual; however, the disease is still progressing, which requires the consideration of treatment options. Donanemab reduced clinical decline in the tau PET SUVr <1.10 population for a certain period of time, which is clinically meaningful.

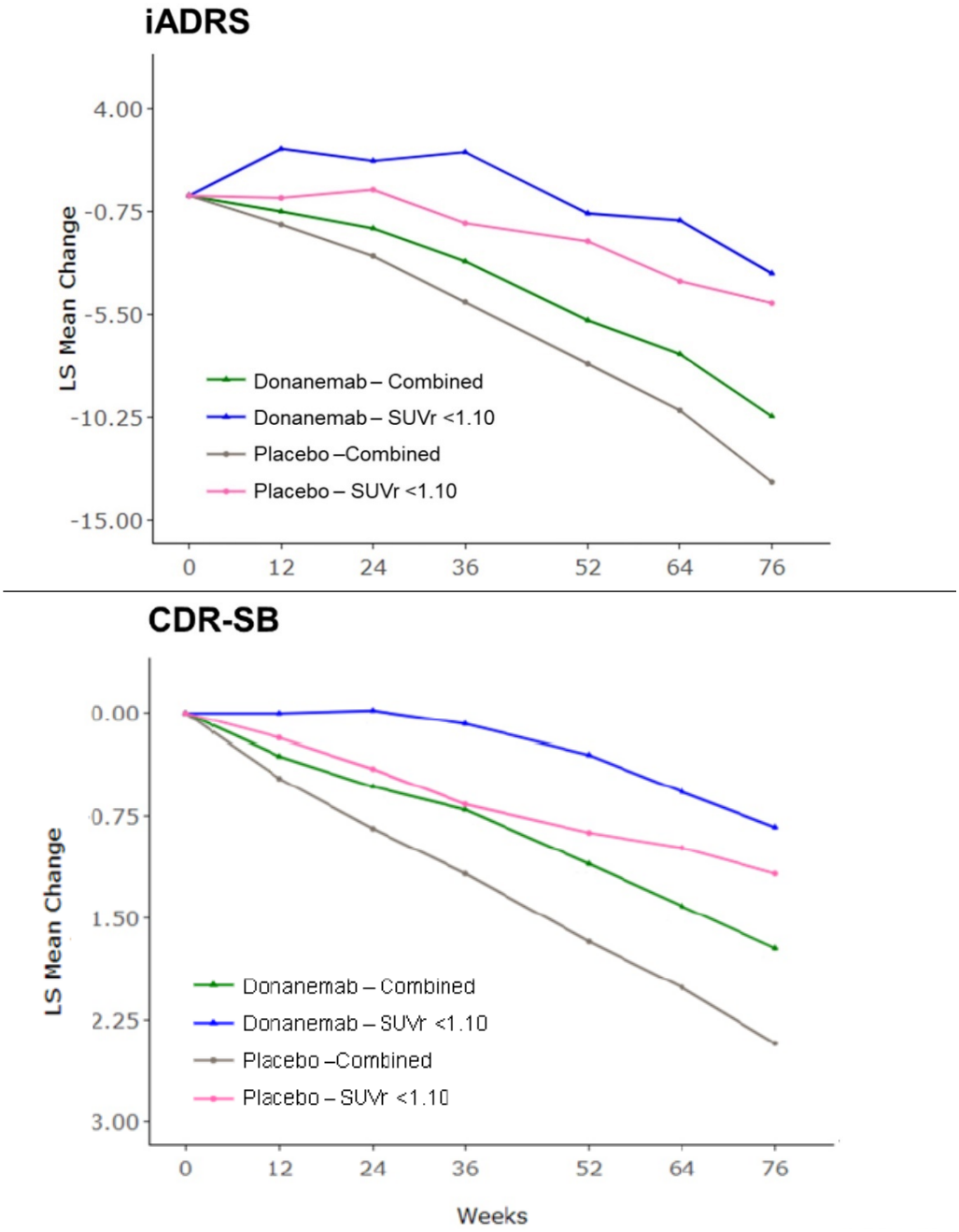


Figure 5. Change from baseline in iADRS and CDR-SB over time in the tau PET SUVr <1.10 population and combined tau PET population in Study AACI (EES)

(SUVr <1.10 = a population in which tau PET SUVr <1.10; Combined = combined tau PET population)

The integrated safety analysis suggests that there is a correlation between the baseline amyloid PET Centiloid values and the risk of ARIA associated with donanemab. Because early AD with no brain tau deposition is found at earlier stages of AD, in which brain Aβ level is assumed to be relatively low, the risk of ARIA associated with donanemab is unlikely to increase in this population compared to the study population in Study AACI. Therefore, the benefit-risk balance is positive for patients with early AD with no brain tau deposition similarly to that for patients with early AD with brain tau deposition.

According to a study in patients with early AD and Aβ positive status, nearly 80% of patients with a clinical diagnosis of MCI due to AD and nearly 90% of patients with a clinical diagnosis of mild AD-D had brain tau deposition as measured by flortaucipir (^{18}F) PET (*Alzheimers Dement.* [N Y] 2023;12:e12372). In addition, visual interpretation of the pattern of flortaucipir (^{18}F) in PET scans corresponded with the tau accumulation Braak stage V or VI (B3) at a high sensitivity and specificity (*JAMA Neurol.* 2020;77:829-39). Conversely, there is a limitation in the capability of regular visual reading to detect tau accumulation corresponding to Braak stage III or IV (B2), and it should be noted that a negative tau PET scan does not always indicate the absence of brain tau accumulation. Furthermore, in Japan, imaging diagnostic tools that are useful for clinical diagnosis of AD have been routinely used in medical practice, and some physicians specialized in treatment of dementia are expected to utilize such tools for the diagnosis of AD before introducing anti-Aβ antibody therapy ("Optimal Use Guidelines for Lecanemab [Genetical Recombination]" PSB/PED Notification No. 1219-2, dated December 19, 2023). Under these circumstances, it is likely that patients have had a clinical diagnosis of "Alzheimer's disease" defined as a category corresponding to the accumulation of amyloid and tau according to the amyloid, tau, neurodegeneration (ATN) classification system (*Alzheimers Dement.* 2018;14:535-62) before their AD pathology is assessed such as by amyloid PET and tau PET.

Based on the above, tau PET is unnecessary before the infusion of donanemab in patients with early AD in whom the presence of brain Aβ has been confirmed.

In view of the results of Study AACI and the results of the above discussions about the intended patient population of donanemab, the proposed indication is "To slow the progression of mild cognitive impairment and mild dementia due to Alzheimer's disease."

PMDA's view:
The efficacy of donanemab was demonstrated in Study AACI conducted in patients with early AD who had findings suggesting the presence of brain Aβ pathology. Based on this result and the mechanism of action of donanemab, brain Aβ pathology should be assessed before the use of donanemab. In addition, based on the applicant's explanation regarding the correlation between CSF testing and PET scan, patients with brain Aβ pathology can be identified by amyloid PET scan, CSF testing, and other testing methods whose results show an established correlation with amyloid pathology, as with the case of the patient population in Study AACI.

PMDA's view on the necessity of confirming the presence of brain tau pathology before the initiation of donanemab treatment:
At present, there are no clinical study data based on the evaluation of the efficacy of donanemab in patients with early AD who have no or very low tau on flortaucipir (^{18}F) PET. In addition, safety data in Study AACI Addendum 9 showed that adverse events including ARIA occurred to a certain extent in the group of patients with no or very low tau on flortaucipir (^{18}F) PET, as with the case of the combined tau level population (Table 76). In the group of patients with no or very low tau on flortaucipir (^{18}F) PET, 4 subjects died (gun shot wound, head injury, death, and pelvic fracture). Among these, the events in 3 subjects (gun shot wound, head injury,

and pelvic fracture) were considered unrelated to the study drug, and the event in the remaining 1 subject was classified as “death” and the causal relationship was “not reported.”

Table 76. Incidence of adverse events in subjects with no or very low tau on flortaucipir (^{18}F) PET and in the combined tau level population in Study AACI Addendum 9 (safety analysis set)

	Donanemab				
	Combined tau level population (N = 1047)	No or very low tau level population (N = 250)	Heterozygous (N = 127)	Homozygous (N = 21)	Non-carrier (N = 101)
Any adverse event	85.0 (890)	82.4 (206)	83.5 (106)	85.7 (18)	80.2 (81)
Death	1.0 (10)	1.6 (4)	0 (0)	0 (0)	4 (4.0)
Serious events	17.3 (181)	16.8 (42)	17.3 (22)	9.5 (2)	17.8 (18)
Treatment discontinuation	7.5 (79)	8.8 (22)	9.4 (12)	14.3 (3)	5.9 (6)
Infusion related reaction	10.0 (105)	7.2 (18)	7.1 (9)	4.8 (1)	6.9 (7)
Any ARIA	30.1 (315)	27.2 (68)	30.7 (39)	57.1 (12)	16.8 (17)
ARIA-E	19.7 (206)	16.8 (42)	19.7 (25)	42.9 (9)	7.9 (8)
ARIA-H	25.1 (263)	23.2 (58)	24.4 (31)	47.6 (10)	16.8 (17)

% (n)

Therefore, donanemab is recommended for a patient population equivalent to the Study AACI population in whom the benefit-risk balance of donanemab has been clarified by the clinical study data. It is desirable to perform a flortaucipir (^{18}F) PET scan before the use of donanemab, and to administer donanemab to patients with early AD whose findings indicate brain tau deposition. However, if the patient’s radiographic and amyloid PET findings and clinical symptoms suggest an advanced state of AD and brain tau deposition, initiation of donanemab without flortaucipir (^{18}F) PET scans may also be an option, given the following factors: (1) A PET scan can pose a risk of radiation exposure to the patient; (2) at present, no standard quantitative evaluation method has been established for tau PET scans; and (3) it has been reported in a study that nearly 80% to 90% of patients with a clinical diagnosis of early AD were confirmed to have brain tau deposition on flortaucipir (^{18}F) PET.

Based on the above, PMDA concluded that cautionary statements including the following should be included in the “Precautions Concerning Indication” section of the package insert, and that information such as key eligibility criteria in Study AACI should be provided using the package insert and information materials.

- Donanemab should be used only in patients diagnosed as having AD based on confirmed findings that suggest the presence of Aβ pathology as measured by approved diagnostic methods, such as amyloid PET and CSF testing.
- Donanemab should not be initiated in asymptomatic persons with findings suggesting only the presence of Aβ pathology, and patients with moderate or severe AD-D.
- The eligibility of patients for donanemab treatment should be determined by only physicians who are fully familiar with the details of the “17. Clinical Studies” section, diagnostic criteria used in Study AACI, the range of clinical symptom scores for patients enrolled in the study, criteria for Aβ pathology and tau pathology, study results, and other information.
- The efficacy and safety of donanemab have not been established in patients whose flortaucipir (^{18}F) PET findings do not show a low tau level or higher. Before initiating donanemab treatment, whether

a flortaucipir (^{18}F) PET scan is necessary should be determined taking into account the test results for Aβ pathology, the stage of AD, and the availability of flortaucipir (^{18}F) PET scan (including the possibility of coordination with medical institutions that can perform such an examination).

PMDA concluded that the applicant's proposed indication is acceptable if the cautionary statements above are included in the labeling.

The appropriateness of the decision above will be finalized taking into account the comments from the Expert Discussion.

7.R.6 Dosage and administration

7.R.6.1 Recommended dosage, dosing interval, and route of administration

The applicant's explanation about the recommended dosage, dosing interval, and route of administration of donanemab:

In Studies AACC and AACD, the greatest reduction in amyloid plaques was observed when donanemab 20 mg/kg was administered intravenously every 4 weeks, and the safety of donanemab was also demonstrated. In Study AACG, the dosage regimen was changed to a fixed dose of 1400 mg (equivalent to 20 mg/kg in patients weighing 70 kg), a dose titration regimen (700 mg for the first 3 doses) was established to prevent the occurrence of ARIA-E-related events, and donanemab was to be administered intravenously every 4 weeks up to Week 72. In Study AACI, donanemab was administered with a dosage regimen[52)] similar to that used in Study AACG. The results of Studies AACG and AACI showed that donanemab statistically significantly slowed clinical decline on iADRS, the primary endpoint, and donanemab tended to consistently slow clinical decline across secondary endpoints, including CDR-SB [see Section "7.R.3 Efficacy"]. The applicant considered that the risks associated with donanemab reported in Studies AACG and AACI were acceptable regardless of ApoE ε4 carrier status [see Section "7.R.4 Safety"].

In Study AACI, if ARIA occurred during the first 3 doses, donanemab 700 mg could be continued thereafter at the discretion of the investigator. Seventeen subjects received donanemab 700 mg as the fourth dose. The baseline characteristics for these subjects were generally similar to those for the donanemab group in the overall population, except for the proportion of *APOE4* homozygous carriers (35.3%, 6 of 17 subjects) compared to that in the donanemab group in the overall population (16.7%, 143 of 857 subjects). Of the 17 subjects who received donanemab 700 mg as the fourth dose, 14 had their dose increased to 1400 mg during the double-blind period, and the remaining 3 subjects continued on 700 mg.

Taken together, the dosage regimen for patients with early AD should be donanemab 700 mg every 4 weeks for the first 3 doses, followed by donanemab 1400 mg every 4 weeks, administered as an intravenous infusion over at least 30 minutes, as done in Studies AACG and AACI. The dosage regimens in Studies AACG and AACI

52) At the start of Study AACI, donanemab was intravenously administered at 1400 mg every 4 weeks. However, serious ARIA-E events were reported in 2 subjects early in the treatment period (during the first 3 doses). The protocol was amended to change the dosage regimen, and donanemab was administered at 700 mg for the first 3 doses in accordance with Protocol version (a) (December 2020).

were established to ensure that amyloid plaque clearance would be achieved earlier by increasing the dose level to 1400 mg. However, taking into account the results from Study AACI, it is also possible to continue donanemab 700 mg for the fourth and subsequent doses in clinical settings based on the medical judgement. In addition to the management of ARIA, cautionary statements regarding a decision to discontinue treatment based on clinical symptoms will be included in the package insert [see Sections "7.R.4.1 Amyloid-related imaging abnormalities" and "7.R.6.3 Decision on early treatment discontinuation based on clinical symptoms"]. In Studies AACG and AACI, subjects whose amyloid PET scan results met the dose cessation criteria were assigned to receive placebo [see Sections "7.3 Foreign phase II study (Study AACG)" and "7.4 Global phase III study (Study AACI)"]; therefore, the time to cease donanemab treatment as well as the decision to cease treatment will be discussed in the next section.

PMDA's view:
In view of the efficacy and safety of donanemab observed in Studies AACG and AACI, the dosage regimen presented by the applicant is acceptable as the recommended dosage regimen provided that cautionary statements regarding ARIA and other anticipated risks associated with donanemab are included in the package insert and information materials in an appropriate manner [see Section "7.R.4 Safety"]. The applicant explained that the majority of subjects who had received 700 mg as the fourth dose had a subsequent dose increase to 1400 mg in Study AACI. Based on the applicant's explanation, PMDA considers that an option to continue donanemab 700 mg for the fourth and subsequent doses based on medical judgement can be selected in clinical settings. However, given the reason why 1400 mg was selected as the recommended dosage in Studies AACG and AACI, the design of Study AACI in which dose reduction to 700 mg was not allowed during the study period, and the extremely small number of subjects who continued to receive 700 mg in Study AACI, the efficacy of donanemab 700 mg without dose titration to 1400 mg is unknown. Based on the above, the "Precautions Concerning Indication" section of the package insert should include a cautionary statement to the effect that if the dose cannot be increased to 1400 mg or cannot continue at 1400 mg for safety-related or other reasons, donanemab treatment at 700 mg should not be continued purposelessly.

The appropriateness of the decision above will be finalized taking into account the comments from the Expert Discussion.

7.R.6.2 Time to cease treatment and decision to cease treatment based on amyloid PET results

The applicant's explanation about the time to cease treatment and decision to cease treatment:
In view of its mechanism of action, donanemab was developed as a therapy that can be ceased in patients in whom amyloid plaque clearance has been achieved based on an evaluation performed at a specific time after the initiation of treatment. In the development of donanemab, amyloid plaque clearance was defined as amyloid plaque level <24.1 Centiloids (corresponding to negativity in autopsy-confirmed data [sparse plaques according to the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) classification][32]) as measured quantitatively by amyloid PET based on florbetapir (^{18}F) data (e.g., *Lancet Neurol.* 2012;11:669-78, *J Nucl Med*. 2015;56:1736-41).

In Study AACI, an amyloid PET scan using florbetapir (^{18}F) or florbetaben (^{18}F) was performed every 6 months to monitor the change in amyloid plaque levels after dose cessation using a numerical scale (Centiloid). Patients who met the amyloid PET criteria (shown below) at Weeks 24, 52, and 76 were switched from donanemab to placebo. A Centiloid value of 11 is an integer established as a level that is almost unlikely to exceed the threshold for amyloid plaque clearance in the reassessment, while a Centiloid value of 25 is the smallest integer that exceeds the threshold for amyloid plaque clearance above.

- <11 Centiloids by any single amyloid PET scan
- ≥11 and <25 Centiloids by 2 consecutive amyloid PET scans

In Study AACI, the amyloid plaque level decreased rapidly by Week 24 after administration of donanemab, and the reduction in amyloid plaque level from Week 52 to Week 76 was relatively small (Table 48). In the donanemab group in the overall population, the proportion of subjects who achieved amyloid plaque clearance at Week 24, Week 52, and Week 76 was 29.7%, 66.1%, and 76.4%, respectively. Figure 6 shows the changes from baseline in iADRS and CDR-SB over time in relation to the different times to cease treatment in the overall population in Study AACI. The results suggest that the slowing of the progression of symptoms continued up to Week 76 in all the groups; and that difference from placebo in the reduction of clinical decline was the greatest in the group in which donanemab treatment was ceased based on the amyloid PET scan results at Week 52. There are potential differences in patient characteristics and other factors between the placebo group and each subgroup in relation to the different times to cease donanemab treatment, and between the subgroups in relation to the different times to cease donanemab treatment. Although such differences preclude any definitive interpretation, given that less amyloid plaque reduction in subjects with lower baseline amyloid plaque levels for a specific period (*JAMA.* 2022;79:1015-24), the amount of amyloid plaque removed will be small even if donanemab treatment is continued after Week 52.

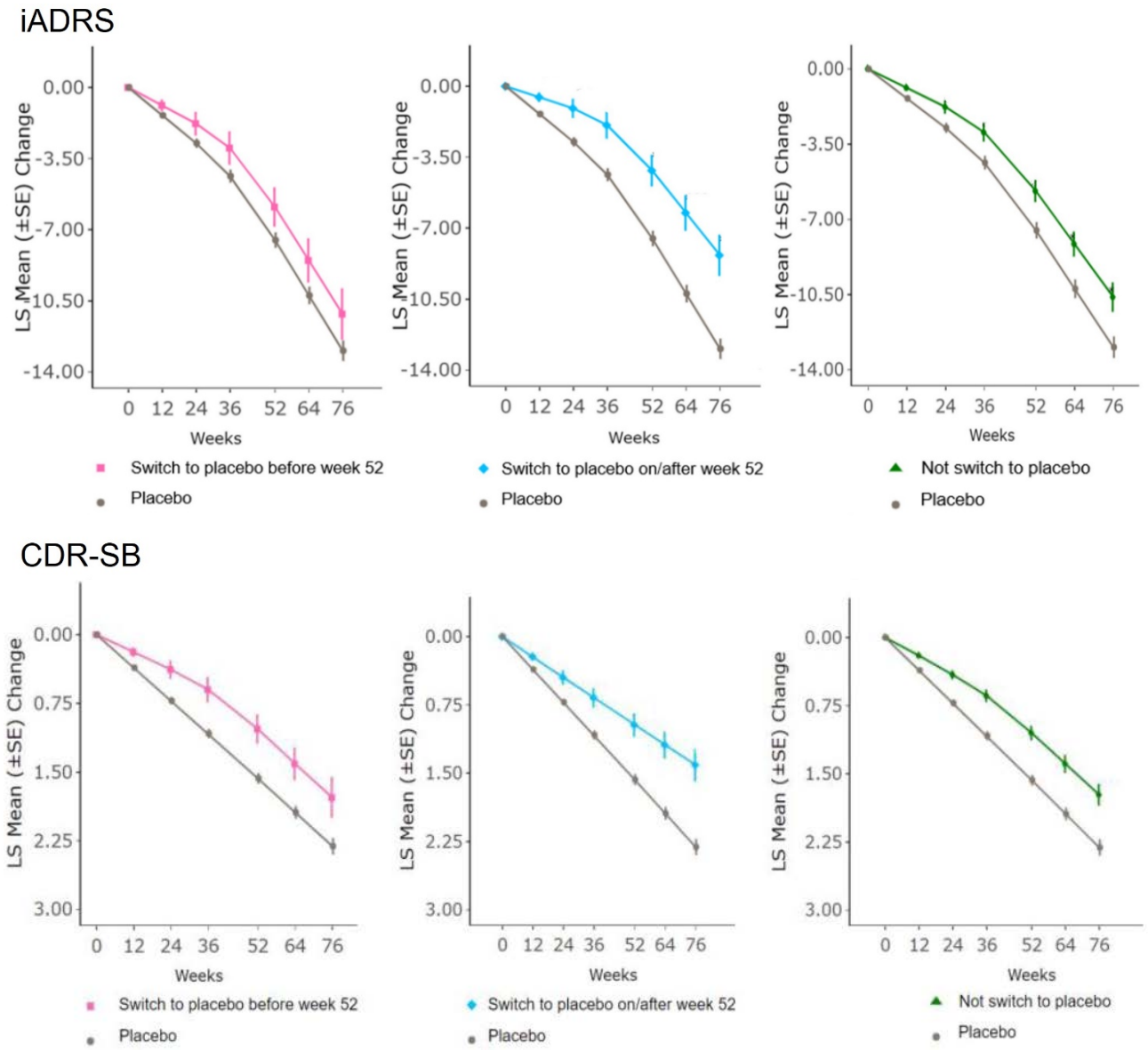


Figure 6. Change from baseline in iADRS and CDR-SB over time in relation to the different times to cease treatment in the overall population in Study AACI (EES)

According to a simulation study of amyloid reaccumulation (*JAMA.* 2022;79:1015-24) based on data from 304 donanemab-treated trial subjects in whom treatment had been ceased after achieving <11 Centiloids at Week 24, the amyloid reaccumulation was estimated to be approximately 3 Centiloids per year, which is consistent with the estimated rate of natural amyloid accumulation (approximately 3.3 Centiloids/year) based on an amyloid reaccumulation modeling study (*Neurol.* 2021;96:e1347-57).

Furthermore, the benefit of administering donanemab after amyloid plaque clearance have been achieved, which is the goal of donanemab therapy, is not clear, and the double-blind period in Study AACI was 76 weeks. Therefore, the “Dosage and Administration” section will state that donanemab treatment is continued until brain amyloid β plaques are cleared. In addition, the “Precautions Concerning Dosage and Administration” section of the package insert will include cautionary statements to the effect that in principle, the treatment

duration of donanemab is for up to 18 months; and if the cessation of donanemab at less than 18 months of treatment upon confirmation of amyloid plaque clearance is considered, an amyloid PET scan needs to be performed at around 12 months of treatment to determine whether to cease treatment based on the status of amyloid plaque clearance. If the clearance status of amyloid plaques cannot be confirmed after a certain period of time has elapsed after the start of treatment, donanemab treatment will not be continued beyond a maximum of 18 months, and in this case, amyloid PET scans will not be necessary. All the types of amyloid PET scan available in Japan have confirmed high sensitivity and specificity for visual read to detect a certain level of amyloid plaques at autopsy (e.g., *Lancet Neurol.* 2012;11:669-78, *Alzheimers Dement.* 2015;11:964-74); therefore, if the imaging data is determined to be Aβ-negative by visual read, it is considered that amyloid plaque clearance has been achieved. Accordingly, whether amyloid plaques have been cleared is determined based on Aβ negativity in the qualitative evaluation by visual read. In clinical practice, donanemab treatment may potentially be continued for more than 18 months based on the change in amyloid plaque over time. The "Precautions Concerning Dosage and Administration" section of the package insert will include a cautionary statement to the effect that if donanemab is administered for a period longer than 18 months, careful consideration is required to decide whether treatment should be continued.

PMDA's view:
Donanemab is administered as an intravenous infusion every 4 weeks, and periodical safety monitoring, such as by MRI scans, is necessary in patients on donanemab treatment. Given a burden on patients, physicians should be advised to regularly consider whether to continue treatment in patients on donanemab treatment to ensure that donanemab is not administered purposelessly in case the pharmacological action of donanemab is no longer effective. Donanemab binds selectively to N3pG Aβ that is considered to be present only in amyloid plaques, and it is unclear whether continuing donanemab treatment after amyloid plaques have been cleared is clinically meaningful. In addition, although the efficacy of donanemab after treatment discontinuation based on Aβ negativity as measured by amyloid PET Centiloid scale was not evaluated beyond Week 76 in Study AACI, evaluation up to Week 76 suggests that the reduction of decline in cognition will continue after the discontinuation of donanemab. Given this fact, donanemab treatment can be ceased if patients reach Aβ negativity after a certain period of treatment. Whether to continue donanemab treatment is determined not solely on the achievement of amyloid plaque clearance as discussed in the next section, and therefore, the phrase "until brain amyloid β plaques are cleared" should be added to the "Precautions Concerning Dosage and Administration" section of the package insert rather than including this phrase in the "Dosage and Administration" section.

Based on the duration of treatment and results in the donanemab treatment period during the double-blind period in Study AACI, it is currently not clear whether continuing donanemab treatment for more than 18 months is clinically meaningful. The applicant plans to include cautionary statements in the package insert to the effect that in principle, the treatment period of donanemab is for up to 18 months; and if treatment cessation at less than 18 months of treatment is considered, an amyloid PET scan should be performed to assess for Aβ negativity at around 12 months of treatment. This plan is appropriate. In the clinical studies, time to cease treatment was determined based on the criteria as measured by the amyloid PET Centiloid scale;

however, based on the applicant's explanation, PMDA concluded that whether patients have reached Aβ negativity can be determined qualitatively by visual read. If donanemab treatment is ceased at 18 months of treatment, an amyloid PET scan at 18 months will not be required. However, a cautionary statement to the following effect is necessary: if considering continuation of donanemab treatment for more than 18 months, physicians should carefully determine whether to continue treatment by reviewing changes in clinical symptoms and in amyloid plaques up to 18 months.

The appropriateness of the decision above will be finalized taking into account the comments from the Expert Discussion.

7.R.6.3 Decision on early treatment discontinuation based on clinical symptoms

The applicant's explanation about the decision on early treatment discontinuation based on clinical symptoms:
The following evaluation was performed based on the results of Study AACI as to whether donanemab treatment should be discontinued in patients whose symptoms progressed rapidly to moderate or severe AD-D during donanemab treatment:
Table 77 shows the baseline characteristics of subjects who experienced progression to moderate or severe AD-D[53)] during the double-blind period in Study AACI ("progression group") and those who did not ("non-progression group"). The results for the clinical symptom endpoints and tau PET SUVr suggest that the baseline AD was more advanced in the progression group than in the non-progression group.

[53)] Defined as baseline CDR-GS <2, and CDR-GS ≥2 at any post-baseline measurement timepoint

Table 77. Baseline characteristics of the progression group and non-progression group in Study AACI (EES)

	Progression group		Non-progression group	
	Placebo (N = 167)	Donanemab (N = 118)	Placebo (N = 666)	Donanemab (N = 689)
Age[a] (years)	73.43 ± 6.44	72.74 ± 6.43	72.77 ± 6.07	72.78 ± 6.03
<65 years[b]	10.2 (17)	15 (12.7)	10.2 (68)	10.3 (71)
≥65 years and <75 years[b]	43.7 (73)	46.6 (55)	47.4 (316)	49.5 (341)
≥75 years[b]	46.1 (77)	40.7 (48)	42.3 (282)	40.2 (277)
ApoE ε4 carrier status				
Carriers[b]	63.9 (106/166)	64.1 (75/117)	73.5 (488/665)	71.4 (491/688)
Heterozygous[b]	51.8 (86/166)	47.9 (56/117)	55.4 (368/665)	54.4 (374/688)
Homozygous[b]	12.0 (20/166)	16.2 (19/117)	18.1 (120/665)	17.0 (117/688)
Non-carriers[b]	36.1 (60/166)	35.9 (42/117)	26.5 (176/665)	28.6 (197/688)
Years since onset of AD[a]	4.06 ± 2.33	4.50 ± 2.67	3.79 ± 2.36	3.82 ± 2.52
Concomitant symptomatic AD medication[b]	76.6 (128)	78.8 (93)	56.5 (376)	57.9 (399)
CDR-SB[a]	5.38 ± 1.56	5.80 ± 1.57	3.31 ± 1.53	3.39 ± 1.61
ADAS-Cog13[a]	35.88 ± 8.13	35.97 ± 8.11	27.18 ± 7.85	26.88 ± 7.80
ADCS-ADL[a]	61.38 ± 8.59	59.77 ± 7.93	68.37 ± 6.70	68.26 ± 7.06
iADRS[a]	92.18 ± 12.73	90.53 ± 12.12	107.42 ± 11.64	107.70 ± 11.69
MMSE[a]	19.40 ± 3.26	19.39 ± 3.51	23.00 ± 3.61	23.20 ± 3.50
CDR-GS				
0[b]	0 (0)	0 (0)	4 (0.6/660)	0.3 (2/678)
0.5[b]	20.4 (34)	16.1 (19)	73.8 (487/660)	71.2 (483/678)
1[b]	79.6 (133)	83.9 (99)	25.6 (169/660)	28.5 (193/678)
Total brain volume (cm^3)	940.52 ± 87.40	961.78 ± 99.37	983.57 ± 99.96	976.11 ± 101.56
Tau PET SUVr	1.48 ± 0.29	1.50 ± 0.27	1.31 ± 0.24	1.32 ± 0.23

[a] Mean ± standard deviation
[b] % (n)

Table 78 shows change from baseline over time in iADRS and CDR-SB up to Week 76 in the progression group and non-progression group in Study AACI (double-blind period). The results suggest that in both groups, donanemab tended to slow the progression of clinical symptoms compared to placebo.

Table 78. Change from baseline over time in iADRS and CDR-SB up to Week 76 in the progression group and non-progression group in Study AACI (double-blind period) (EES)

	Progression group		Non-progression group	
	Placebo	Donanemab	Placebo	Donanemab
iADRS				
Baseline[a]	92.18 ± 12.73 (N = 165)	90.50 ± 12.18 (N = 111)	107.63 ± 11.58 (N = 638)	107.91 ± 11.21 (N = 645)
Change from baseline at Week 12 (MMRM)[b, c]	−5.27 ± 0.58	−5.19 ± 0.71	0.36 ± 0.27	0.70 ± 0.27
Change from baseline at Week 24 (MMRM)[b, c]	−9.05 ± 0.65	−7.44 ± 0.80	−0.46 ± 0.32	0.26 ± 0.32
Change from baseline at Week 36 (MMRM)[b, c]	−13.37 ± 0.70	−10.77 ± 0.86	−2.05 ± 0.34	−0.88 ± 0.35
Change from baseline at Week 52 (MMRM)[b, c]	−20.28 ± 0.81	−17.11 ± 0.97	−3.71 ± 0.40	−2.80 ± 0.40
Change from baseline at Week 64 (MMRM)[b, c]	−23.76 ± 0.93	−21.98 ± 1.12	−5.50 ± 0.46	−3.74 ± 0.47
Change from baseline at Week 76 (MMRM)[b, c]	−30.24 ± 1.03	−27.59 ± 1.24	−7.97 ± 0.51	−6.01 ± 0.51
CDR-SB				
Baseline[a]	5.38 ± 1.561 (N = 167)	5.79 ± 1.577 (N = 117)	3.29 ± 1.530 (N = 649)	3.39 ± 1.603 (N = 656)
Change from baseline at Week 12 (MMRM)[b, c]	1.50 ± 0.10	1.04 ± 0.12	0.15 ± 0.05	0.10 ± 0.05
Change from baseline at Week 24 (MMRM)[b, c]	2.10 ± 0.11	1.58 ± 0.13	0.42 ± 0.05	0.25 ± 0.05
Change from baseline at Week 36 (MMRM)[b, c]	2.96 ± 0.11	2.34 ± 0.14	0.61 ± 0.06	0.30 ± 0.06
Change from baseline at Week 52 (MMRM)[b, c]	4.24 ± 0.13	3.61 ± 0.16	0.87 ± 0.07	0.50 ± 0.07
Change from baseline at Week 64 (MMRM)[b, c]	5.05 ± 0.14	4.34 ± 0.17	1.08 ± 0.07	0.74 ± 0.07
Change from baseline at Week 76 (MMRM)[b, c]	5.84 ± 0.16	5.17 ± 0.19	1.40 ± 0.08	0.95 ± 0.08

[a] Mean ± standard deviation
[b] An MMRM with treatment, visit, treatment-by- visit interaction, baseline value, baseline value-by-visit interaction, baseline age, baseline brain tau level (low/medium or high), pooled site, and baseline symptomatic AD medication (ChE inhibitor and/or memantine) use as fixed effects. An unstructured variance-covariance matrix was used for within-subject effects.
[c] Least squares mean ± standard error

According to an analysis for the progression group in Study AACI (double-blind period), the reduction in brain Aβ deposition from baseline as measured by the amyloid PET Centiloid scale from Week 24 to Week 76 was greater in the donanemab group than in the placebo group (Table 79).

Table 79. Change from baseline over time in amyloid PET Centiloid scale in the progression group in Study AACI (double-blind period) (EES)

	Progression group		Non-progression group	
	Placebo	Donanemab	Placebo	Donanemab
Baseline[a]	102.15 ± 30.718 (N = 161)	99.58 ± 33.476 (N = 113)	101.75 ± 35.132 (N = 630)	104.24 ± 34.240 (N = 633)
Change from baseline at Week 24 (MMRM)[b, c]	−0.13 ± 1.95	−61.23 ± 2.35	0.23 ± 0.95	−63.23 ± 0.95
Change from baseline at Week 52 (MMRM)[b, c]	−2.30 ± 2.02	−80.20 ± 2.42	−0.65 ± 0.99	−83.35 ± 1.00
Change from baseline at Week 76 (MMRM)[b, c]	−1.37 ± 2.09	−85.13 ± 2.52	−0.35 ± 1.02	−87.10 ± 1.03

[a] Mean ± standard deviation
[b] An MMRM with treatment, visit, treatment-by- visit interaction, baseline value, baseline value-by- visit interaction, baseline age, baseline brain tau level (low/medium or high), pooled site, and baseline symptomatic AD medication (ChE inhibitor and/or memantine) use as fixed effects. An unstructured variance-covariance matrix was used for within-subject effects.
[c] Least squares mean ± standard error

In Study AACI (double-blind period), the change (least squares mean) in iADRS and CDR-SB from the time of progression to moderate or severe AD-D to final assessment timepoint in the progression group was −10.5 (iADRS) and 0.53 (CDR-SB) in the placebo group and −11.3 (iADRS) and 0.12 (CDR-SB) in the donanemab group. The degree of decline on iADRS was greater in the donanemab group than in the placebo group. However, there may be a group bias due to uneven distribution of patient characteristics in the progression group; therefore, the efficacy of continued donanemab treatment in patients who experienced progression to moderate or severe AD-D cannot be evaluated based on the results of an exploratory analysis using data from this subgroup.

In Study AACI, an analysis of data from patients whose MMSE scores declined to a level corresponding to moderate AD-D (MMSE <20) from screening to baseline showed that donanemab tended to slow the progression of clinical symptoms compared to placebo [see Section “7.R.3.2 Factors affecting efficacy,” Table 47].

Taken together, not only the severity of AD-D but also the course of clinical symptoms and other aspects should be taken into account to determine whether to continue donanemab therapy in patients being treated with donanemab; therefore, the following cautionary statement should be included in the “Precautions Concerning Dosage and Administration” section of the package insert:

- During treatment with donanemab, perform cognition tests as well as clinical symptoms assessment based on interviews with patients and their family members and/or caregivers on subjective and objective symptoms approximately every 6 months and determine whether to continue treatment based on the assessment results. Even when an amyloid PET scan has been performed, the decision should be made based on a comprehensive assessment taking into account clinical symptoms. If the course of clinical symptoms, severity of dementia, and other factors are unlikely to indicate the efficacy of donanemab, discontinue treatment with donanemab.

PMDA's view:
The exploratory analysis assessed a group of patients who experienced progression to moderate or severe AD-D during donanemab treatment in Study AACI, and there is a limitation in the evaluation of the efficacy of donanemab in such patient population. Therefore, cautionary statements to the following effect should be included: whether to continue donanemab treatment should be determined in a comprehensive manner taking into account the course of clinical symptoms, the rate of disease progression, and other factors, in addition to the results of amyloid PET scans; the efficacy of donanemab is not established when treatment is continued in patients who experienced progression to moderate or severe AD-D during donanemab treatment.

The appropriateness of the decision above will be finalized taking into account the comments from the Expert Discussion.

7.R.7 Post-marketing investigations

The applicant's explanation about the post-marketing investigations of donanemab:
The applicant has planned to conduct a specified use-results survey enrolling all patients who have initiated donanemab treatment within 1.5 years after the start of surveillance to investigate the occurrence of ARIA and serious hypersensitivity associated with the use of donanemab in clinical settings. The survey will consist of a follow-up period of up to 24 months (patients with ARIA, however, will be followed up for an additional 6-month period beginning on the day of onset of ARIA). It is estimated that a sample size of 1,000 patients is necessary to detect an increase in the risk of ARIA-E, with a statistical power of ≥95%, assuming that the incidence of symptomatic ARIA-E in routine clinical practice, which is targeted by this survey, is 1.5 times the incidence of symptomatic ARIA-E in the clinical study (5.8%). The applicant considers that the sample size can be achieved by gathering data from all patients who have initiated donanemab treatment within 1.5 years after the start of the survey. The survey is planned to gather various types of information, namely, details of ApoE ε4 carrier status and concomitant antithrombotic use, which may affect the occurrence of ARIA; results of head MRI scans performed prior to the initiation of donanemab treatment; results of Aβ pathology and tau PET scans; and other patient characteristics-related information important for identifying the pathological condition of patients with AD. If a certain number of ARIA events occur during the survey, the data gathered will allow investigation of factors that can be related to ARIA.

PMDA's view:
Since serious adverse events associated with ARIA and hypersensitivity reaction occurred in the clinical studies, the applicant should conduct post-marketing surveillance to gather information on the incidence of ARIA-related events and hypersensitivity reaction-related events associated with the use of donanemab in clinical settings and analyze their risk factors. The current post-marketing surveillance plan is generally appropriate. The safety and efficacy of donanemab in patients after treatment cessation or patients who continued treatment for more than 18 months should be evaluated by including the result data from ongoing Study AACI. The details of the post-marketing surveillance, including the identification of safety specification, adequacy of risk classification, and the appropriateness of pharmacovigilance activities and risk minimization activities, will be finalized in accordance with the "Risk Management Plan Guidance" (PFSB/SD Notification No. 0411-

1, and PFSB/ELD Notification No. 0411-2, dated April 11, 2012) taking into account the comments from the Expert Discussion.

8. Results of Compliance Assessment Concerning the New Drug Application Data and Conclusion Reached by PMDA

8.1 PMDA's conclusion concerning the results of document-based GLP/GCP inspections and data integrity assessment

The investigation is currently underway. The results and conclusion by PMDA will be reported in Review Report (2).

8.2 PMDA's conclusion concerning the results of the on-site GCP inspection

The investigation is currently underway. The results and conclusion by PMDA will be reported in Review Report (2).

9. Overall Evaluation during Preparation of the Review Report (1)

On the basis of the data submitted, PMDA has concluded that donanemab has efficacy in slowing the progression of MCI due to AD and mild AD-D, and that donanemab has acceptable safety in view of its benefits. It is clinically meaningful to make donanemab available in clinical settings as a new option for the treatment of MCI due to AD and mild AD-D. Issues that need further discussion include efficacy, dosage and administration, cautionary statements in the package insert, and post-marketing investigations.

PMDA has concluded that donanemab may be approved if donanemab is not considered to have any particular problems based on comments from the Expert Discussion.

Review Report (2)

July 17, 2024

Product Submitted for Approval

Brand Name	Kisunla Intravenous Infusion 350 mg
Non-proprietary Name	Donanemab (Genetical Recombination)
Applicant	Eli Lilly Japan K.K.
Date of Application	August 18, 2023

List of Abbreviations

See Appendix.

1. Content of the Review

Comments made during the Expert Discussion and the subsequent review conducted by the Pharmaceuticals and Medical Devices Agency (PMDA) are summarized below. The expert advisors present during the Expert Discussion were nominated based on their declarations, etc. concerning the product submitted for marketing approval, in accordance with the provisions of the Rules for Convening Expert Discussions, etc. by Pharmaceuticals and Medical Devices Agency (PMDA Administrative Rule No. 8/2008 dated December 25, 2008).

Unless otherwise specified, "MCI due to AD and mild AD-D" are collectively referred to as "early AD" in the sections shown below [see Appendix].

1.1 Efficacy

While the results of Study AACI failed to verify the disease-modifying effect of donanemab, the expert advisors supported the PMDA's conclusions that the data demonstrated the efficacy of donanemab in patients with early AD. The following comments were made by the expert advisors:

- No biomarkers indicating the efficacy of donanemab have been identified so far, and further investigation is desirable.
- Regarding the efficacy data in Study AACI, not only the results for the overall population but also the subgroup analysis results by brain tau level should be provided using the materials for healthcare professionals.

1.2 Safety

At the Expert Discussion, the expert advisors supported the PMDA's conclusions presented in Section "7.R.4 Safety" in Review Report (1), including the following conclusion: it is acceptable to include patients with early AD with severe white matter disease in the intended patient population. The following comments were made by the expert advisors:

- Because white matter disease is observed in patients with vascular dementia and other types of dementia for which donanemab is not indicated, differential diagnosis should be performed prior to the initiation of donanemab treatment. The plan to include the following cautionary statement in the "Warnings" section of the package insert is reasonable: Donanemab should only be administered to patients who are determined to be eligible for its use by physicians with sufficient knowledge and experience regarding the pathology, diagnosis, and treatment of AD.
- The applicant plans to ensure safety in ApoE ε4 carriers by advising physicians of the increased ARIA risk in such patient population and then performing patient monitoring for ARIA as with the case of non-carrier patients. This plan is considered appropriate at this point. However, because the patient's *APOE* genotype is likely to influence the patient's decision on treatment, it is desirable that *APOE* genotype testing will be available in clinical settings.
- CAA is inferred to be closely associated with the development of ARIA, and poorly controlled hypertension is expected to increase the risk of developing ARIA and the risk of severe ARIA. Therefore, further investigation regarding the relationship between hypertension and the incidence or worsening of ARIA is desirable.

PMDA's conclusion based on the review in Section "7.R.4 Safety" in Review Report (1) and discussions at the Expert Discussion:

- The applicant should gather post-marketing data on the incidence of ARIA by ApoE ε4 carrier status and the effects of elevated blood pressure on the incidence and worsening of ARIA. Based on the gathered information, the applicant should consider measures to ensure the proper use of donanemab.
- The following issues should be included in the package insert and other materials to raise awareness:

Warnings

- Donanemab should only be administered to patients who are determined to be eligible for its use by physicians with sufficient knowledge and experience regarding the pathology, diagnosis, and treatment of AD who can manage and explain the risks associated with donanemab at healthcare facilities capable of providing amyloid PET, MRI scans, and other examinations required for donanemab treatment, and their management, or at healthcare facilities coordinating with such healthcare facilities.
- Prior to initiating treatment with donanemab, patients and their families/caregivers should be fully informed of the incidence of ARIA associated with donanemab, the risk of ARIA and examinations needed for risk management, and actions to be taken in the event of ARIA. Treatment should be started only after written consent has been obtained. Instruct the patients and their families/caregivers to contact the primary care physician immediately if any abnormality is noted.

Contraindication (excerpted descriptions relevant to this section)

- Patients with findings that show the presence of vasogenic cerebral edema prior to the initiation of donanemab treatment
- Patients with findings that show the presence of ≥5 cerebral microhemorrhages, superficial siderosis, or cerebral hemorrhage >1 cm prior to the initiation of donanemab treatment

Precautions Concerning Dosage and Administration (excerpted descriptions relevant to this section)

- In patients who have severe ARIA-E on MRI or symptomatic ARIA-E, interrupt or discontinue treatment of donanemab. In patients who have asymptomatic, moderate ARIA-E on MRI, interrupt donanemab treatment. In patients who have asymptomatic, mild ARIA-E on MRI, conduct a careful clinical assessment to consider whether to continue donanemab treatment. If treatment is continued, monitor the patient with increased vigilance. If resolution of ARIA symptoms and resolution of ARIA-E on MRI are confirmed after treatment interruption, resumption of treatment may be considered.
- In patients who have severe ARIA-H on MRI or symptomatic ARIA-H, interrupt or discontinue donanemab treatment. In patients who have asymptomatic, moderate ARIA-H on MRI, interrupt donanemab treatment. In patients who have asymptomatic, mild ARIA-H on MRI, conduct a careful clinical assessment to consider whether to continue donanemab treatment. If treatment is continued, monitor the patient with increased vigilance. If resolution of ARIA symptoms and stabilization of ARIA-H on MRI are confirmed after treatment interruption, resumption of treatment may be considered. In patient who have cerebral hemorrhage >1 cm, discontinue donanemab treatment.

Important Precautions (excerpted descriptions relevant to this section)

- Donanemab should be used by physicians with adequate knowledge on the management of ARIA. Before and during the treatment with donanemab, caution should be exercised regarding the following:

- Before initiating donanemab treatment, examine the latest (within 1 year) MRI images for the presence of any abnormal finding including ARIA.
- Most ARIA events occur within the first 24 weeks of donanemab treatment and the majority of serious events of ARIA occurred within the first 12 weeks of donanemab treatment. During the periods, monitor the patient's condition with high vigilance. In patients who have any symptom suggestive of ARIA, conduct a clinical assessment and perform MRI scans, as necessary.
- Even in patients who have no symptoms suggestive of ARIA, perform periodic MRI monitoring for the presence of any ARIA, namely prior to the second dose, dose titration (usually, prior to the fourth dose), the seventh dose, and thereafter. Since the majority of serious ARIA events occur within the first 12 weeks of donanemab treatment, MRI monitoring prior to the third dose of donanemab is desirable, as necessary.
- In APOE ε4 (homozygous or heterozygous) carrier patients, ARIA-E, ARIA-H, serious ARIA-E, and serious ARIA-H events occur more frequently. The incidence of such events is the highest in APOE ε4 homozygous carriers, followed by APOE ε4 heterozygous carriers, and then APOE ε4 non-carriers. Make sure to implement ARIA management including the MRI scans specified above, regardless of the APOE ε4 status. The proportion of APOE ε4 homozygous carriers was 16.7% in Study AACI conducted in patients with early AD.

- Donanemab have never been used in patients with baseline MRI findings that show the presence of severe white matter disease. Whether donanemab can be administered to patients with findings that show the presence of severe white matter disease should be determined carefully taking into account the risks and benefits of donanemab.

- In general, hypertension is a risk factor for cerebral hemorrhage. Before administering donanemab, check whether the patient has elevated blood pressure. Exercise caution when administering donanemab to patients with elevated blood pressure. During donanemab treatment, manage blood pressure properly.

1.3 Intended patient population and indication

Based on the discussions in Section "7.R.5 Intended patient population and indication of donanemab" in Review Report (1), donanemab is recommended for patients with low tau level or higher. Given this, PMDA considered that a cautionary statement should be included in the package insert to the following effect: The efficacy and safety of donanemab have not been established in patients with flortaucipir (^{18}F) PET findings that do not show a low tau level or higher. Conversely, for the reasons outlined in Section "7.R.5 Intended patient population and indication of donanemab," PMDA concluded that instead of requiring flortaucipir (^{18}F) PET scans in every patient before the initiation of donanemab treatment, a cautionary statement to the following effect should be included: before initiating donanemab treatment, whether a flortaucipir (^{18}F) PET scan is necessary should be determined taking into account the test results for Aβ pathology, the stage of AD, the availability of flortaucipir (^{18}F) PET scan.

At the Expert Discussion, the expert advisors generally supported PMDA's conclusions as stated above. The following comments were made by the expert advisors:

- The description of the cautionary statements in the package insert is desirably arranged so as to clarify how flortaucipir (^{18}F) PET scan results are used for donanemab treatment. The information should be provided using appropriate materials.

In light of the above discussions at the Expert Discussion, PMDA concluded that the indication of donanemab should be "to slow the progression of mild cognitive impairment and mild dementia due to Alzheimer's disease," and the points shown below should be included in the "Precautions Concerning Indication" section of the package insert.

Precautions Concerning Indication (excerpted descriptions relevant to this section)

- Donanemab should be used only in patients diagnosed as AD based on confirmed findings suggesting the presence of Aβ pathology as measured by approved diagnostic methods, such as amyloid PET and CSF testing.
- Donanemab treatment should not be initiated in asymptomatic persons with findings suggesting only the presence of Aβ pathology, and patients with moderate or severe AD-D.
- The eligibility of patients for donanemab treatment should be determined by only physicians who are fully familiar with the details of the "17. Clinical Studies" section, diagnostic criteria used in Study AACI, the range of clinical symptom scores for patients enrolled in the study, study results, and other information.
- The efficacy and safety of donanemab have not been established in patients whose flortaucipir (^{18}F) PET findings do not show low tau level or higher. Before initiating donanemab treatment, whether donanemab can be used in the patient should be determined taking into account clinical information

including test results for Aβ pathology, the stage of AD, and the results of flortaucipir (^{18}F) PET scan (if it is performed).

1.4 Dosage and administration

At the Expert Discussion, the expert advisors supported the PMDA's conclusions presented in Section "7.R.6 Dosage and administration" section in Review Report (1), which include the following: in principle, the treatment duration of donanemab is for up to 18 months; and treatment may be ceased if amyloid plaque clearance has been confirmed by amyloid PET scan. The following comments were made by the expert advisors:

- It is expected that Aβ continues to be produced in the brain of patients with AD, and there is a limitation in data obtained during the evaluation period in Study AACI. Therefore, the applicant needs to accrue more data on issues such as the change in symptoms over time after donanemab treatment cessation and the status of reaccumulation of amyloid plaques.
- A testing method used in Study AACI to confirm the clearance of amyloid plaques was amyloid PET scan. Because the correlation between amyloid PET scan results and CSF test results is unknown where amyloid plaques have been removed by anti-Aβ antibody treatment, testing with amyloid PET scan alone is reasonable.

PMDA's conclusion based on the review in Section "7.R.6 Dosage and administration" in Review Report (1) and on discussions at the Expert Discussion:

- The dosage and administration should be as follows: "The usual adult dosage of donanemab (genetical recombination) is 700 mg administered as an intravenous infusion over at least 30 minutes every 4 weeks for the first 3 doses, and then 1400 mg every 4 weeks."
- The following cautionary statements should be included in the package insert and other information materials.

Precautions Concerning Dosage and Administration (excerpted descriptions relevant to this section)

- If the dose cannot be increased to 1400 mg for safety-related or other reasons, donanemab treatment should not be continued purposelessly.
- If clearance of amyloid β plaques is confirmed during donanemab treatment, cease donanemab treatment immediately. Even if clearance of amyloid β plaques is not confirmed, in principle, cease donanemab treatment within 18 months of treatment. If considering continuation of donanemab treatment for more than 18 months, carefully determine whether to continue treatment by reviewing the incidence of adverse reactions at 18 months and changes in clinical symptoms over time and in amyloid β plaques up to 18 months.
- The clearance of amyloid β plaques should be evaluated by amyloid PET scan or equivalent diagnostic methods. Testing should be performed, if necessary, at around 12 months of donanemab treatment.
- During treatment with donanemab, perform cognition tests as well as clinical symptoms assessment based on interviews with patients and their family members and/or caregivers on subjective and objective

symptoms approximately every 6 months. If the course of clinical symptoms, severity of dementia, and other factors are unlikely to indicate the efficacy of donanemab, discontinue treatment with donanemab. The efficacy of donanemab is not established when treatment is continued in patients who experienced progression to moderate or severe dementia during donanemab treatment.

1.5 Risk management plan (draft)

In view of the discussions presented in Section "7.R.7 Post-marketing investigations" in Review Report (1), Section 1.2 in the Review Report (2), and comments from the expert advisers at the Expert Discussion, PMDA considers that post-marketing all-case surveillance should be conducted to cover all patients receiving donanemab until the safety of donanemab is confirmed to a certain extent.

On the basis of the discussion above, PMDA has concluded that the risk management plan (draft) for donanemab should include the safety and efficacy specifications presented in Table 80, and that the applicant should conduct the additional pharmacovigilance activities and risk minimization activities presented in Table 81 and specified use-results survey presented in Table 82.

Table 80. Safety and efficacy specifications in the risk management plan (draft)

Safety specification		
Important identified risks	Important potential risks	Important missing information
• ARIA-E • ARIA-H • Serious hypersensitivity reaction (including infusion related reaction)	• Serious cerebral hemorrhage due to concomitant antithrombotic medication use	None
Efficacy specification		
None		

Table 81. Summary of additional pharmacovigilance activities and additional risk minimization activities included under the risk management plan (draft)

Additional pharmacovigilance activities	Additional risk minimization activities
• Early post-marketing phase vigilance • Specified use-results survey (all-case surveillance)	• Disseminate data gathered during early post-marketing phase vigilance • Prepare and distribute information materials for healthcare professionals (proper use guide) • Prepare and distribute information materials for patients and their family members • Prepare and distribute materials for patients (patient's medical information card) • Confirmation of proper use

Table 82. Outline of specified use-results survey (draft)

Objective	To confirm the safety and efficacy of donanemab used in clinical settings
Survey method	Central registry (all-case surveillance)
Population	Patients with early AD who are treated with donanemab
Observation period	Up to 24 months after the initiation of donanemab treatment. For patients who have developed ARIA-E or ARIA-H, an additional observation period of 6 months from the onset is provided.
Planned sample size	All patients who start donanemab during the planned enrollment period (1.5 years[a])
Main survey items	ARIA-E, ARIA-H, patient characteristics (e.g., sex, age, medical history, comorbidities, disease stage, ApoE ε4 carrier status, results of flortaucipir [^{18}F] PET scan), concomitant antithrombotic medications, clinical symptom assessment of early AD, method for assessing Aβ pathology

[a] The period should be reviewed as necessary based on the status of patient enrollment in the survey.

2. Results of Compliance Assessment Concerning the New Drug Application Data and Conclusion Reached by PMDA

2.1 PMDA's conclusion concerning the results of document-based GLP/GCP inspections and data integrity assessment

The new drug application data were subjected to a document-based inspection and a data integrity assessment in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices. On the basis of the inspection and assessment, PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted.

2.2 PMDA's conclusion concerning the results of the on-site GCP inspection

The new drug application data (CTD 5.3.5.1.2) were subjected to an on-site GCP inspection, in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices. On the basis of the inspection, PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted.

3. Overall Evaluation

As a result of the above review, PMDA has concluded that the product may be approved for the indication and dosage and administration shown below, with the following approval conditions. Since the product is a drug with a new active ingredient, the re-examination period is 8 years. The product is classified as a biological product. The drug substance and drug product are both classified as powerful drugs.

Indication

To slow the progression of mild cognitive impairment and mild dementia due to Alzheimer's disease

Dosage and Administration

The usual adult dosage of donanemab (genetical recombination) is 700 mg administered as an intravenous infusion over at least 30 minutes every 4 weeks for the first 3 doses, and then 1400 mg every 4 weeks.

Approval Conditions

1. The applicant is required to develop and appropriately implement a risk management plan.
2. The applicant is required to conduct a post-marketing use-results survey covering all patients treated with the product to obtain information on patient characteristics until data from a specified number of patients have been accrued. Furthermore, the applicant should gather data on the safety and efficacy of the product early and take appropriate measures to ensure the proper use of the product.

Appendix

List of Abbreviations

Aβ	Amyloid β
$Aβ_{p3-x}$	N-terminal pyroglutamyl amyloid β peptides (3-x)
AD	Alzheimer's disease
ADA	Anti-drug antibodies
ADAS-Cog13	Alzheimer's Disease Assessment Scale-13-item Cognitive subscale
ADCP	Antibody dependent cellular phagocytosis
ADCS-iADL	Alzheimer's Disease Cooperative Study-Activities of Daily Living Inventory, instrumental items
AD-D	Alzheimer's disease dementia
AE	Adverse event
ANCOVA	Analysis of covariance
ApoE ε4	Apolipoprotein E ε4
APP	Amyloid precursor protein
ARIA	Amyloid-related imaging abnormalities
ARIA-E	Amyloid related imaging abnormalities-edema/effusion
ARIA-H	Amyloid related imaging abnormalities-hemorrhage or superficial siderosis
AST	Aspartate aminotransferase
AUC	Area under the concentration versus time curve
AUC_{0-inf}	AUC from zero to infinity
AUC_{0-x}	AUC from time zero to fixed time x
AUC_{τ}	AUC during 1 dosing interval
$AUC_{\tau, ss}$	AUC during 1 dosing interval at steady state
BA	Bioavailability
BMI	Body mass index
C1q	Complement component 1, q subcomponent
CAA	Cerebral amyloid angiopathy
CAL	Cells at the limit of *in vitro* cell age
cDNA	Complementary DNA
CDR	Clinical Dementia Rating
CDR-GS	Clinical Dementia Rating Scale-Global Score
CDR-SB	Clinical Dementia Rating-Sum of Boxes
CE-SDS	Capillary Electrophoresis-sodium dodecyl sulphate
ChE	Cholinesterase
CHO cells	Chinese hamster ovary cells
CI	Confidence interval
cIEF	Capillary isoelectric focusing
CL	Total body clearance
CL/F	Apparent total body clearance
C_{max}	Maximum observed drug concentration
$C_{max, ss}$	C_{max} during a dosing interval at steady state
$C_{min, ss}$	Drug concentration before the next dose at steady state
CNS	Central nervous system
COVID-19	Coronavirus Disease 2019
CQA	Critical quality attribute
CrCL	Creatinine clearance
CSF	Cerebrospinal fluid
C-SSRS	Columbia Suicide Severity Rating Scale
CTD	Common technical document
DNA	Deoxyribonucleic acid

Donanemab	Donanemab (genetical recombination)
Donepezil	Donepezil hydrochloride
DPM	Disease progression model
Early AD	Mild cognitive impairment due to Alzheimer's disease (MCI due to AD) and mild Alzheimer's disease dementia (AD-D)
EES	Evaluable Efficacy Set
ELISA	Enzyme-linked immunosorbent assay
Fab	Antigen-binding fragment
FAS	Full analysis set
FcγR	Fc gamma receptor
FcRn	Neonatal Fc receptor
FCSRT-IR	Free and Cued Selective Reminding Test with Immediate Recall
Galantamine	Galantamine hydrobromide
GFAP	Glial fibrillary acidic protein
HCP	Host cell protein
iADRS	Integrated Alzheimer's Disease Rating Scale
ICH Q5A (R1) guidelines	"Viral Safety Evaluation of Biotechnology Products Derived from Cell Lines of Human or Animal Origin" (PMSB/ELD Notification No. 329, dated February 22, 2000)
ICH Q5B guidelines	"Quality of Biotechnological Products: Analysis of the Expression Construct in Cells Used for Production of R-DNA Derived Protein Products" (PMSB/ELD Notification No. 3, dated January 6, 1998)
ICH Q5D guidelines	"Derivation and Characterisation of Cell Substrates Used for Production of Biotechnological/Biological Products" (PMSB/ELD Notification No. 873, dated July 14, 2000)
ICH Q5E guidelines	"Comparability of Biotechnological/Biological Products Subject to Changes in Their Manufacturing Process" (PFSB/ELD Notification No. 0426001 dated April 26, 2005)
ICU	Intensive care unit
IgG	Immunoglobulin G
IRR	Infusion-related reaction
ITT	Intent-to-treat
Kisunla	Kisunla Intravenous Infusion
Lecanemab	Lecanemab (genetical recombination)
LLT	Lowest level terms
LS	Least squares
MAD	Multiple ascending dose
MCB	Master cell bank
MCID	Minimal clinically important difference
MCI due to AD	Mild cognitive impairment due to Alzheimer's disease
MedDRA	Medical dictionary for regulatory activities
Memantine	Memantine hydrochloride
MMRM	Mixed Model for Repeated Measures
MMSE	Mini-Mental State Examination
MRI	Magnetic resonance imaging
N3pG Aβ	Pyroglutamate modified amyloid β at the third amino acid of amyloid β
NCS	Natural cubic spline
NCS2	Natural cubic spline model with 2 degrees of freedom
NFAT	Nuclear factor of activated T cells
NfL	Neurofilament light chain
NMDA	*N*-methyl-D-aspartate
PBS	Phosphate-buffered saline
PD	Pharmacodynamics

PET	Positron emission tomography
PK	Pharmacokinetics
PMDA	Pharmaceuticals and Medical Devices Agency
PPK	Population pharmacokinetics
PT	Preferred term
p-tau	Phosphorylated tau
Q	Inter compartment clearance
Q2W	Quaque 2 weeks
Q4W	Quaque 4 weeks
QOL	Quality of life
RH	Relative humidity
rt-PA	Recombinant tissue-type plasminogen activator
SAD	Single-ascending dose
SAE	Serious adverse event
SE	Standard error
SEC	Size exclusion chromatography
SMQ	Standardised MedDRA queries
SOC	System organ class
SUVr	Standardized uptake value ratio
$t_{1/2}$	Half-life
TEAE	Treatment-emergent adverse event
Time-PMRM	Time-progression model with repeat measure
t_{max}	Time of maximum observed drug concentration
V_c	Central volume of distribution
V_p	Peripheral volume of distribution
V_{ss}	Volume of distribution at steady state
V_z	Volume of distribution
V_z/F	Apparent volume of distribution
WCB	Working cell bank