Report on the Deliberation Results

August 25, 2023
Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau
Ministry of Health, Labour and Welfare

Brand Name	Leqembi for Intravenous Infusion 200 mg
	Leqembi for Intravenous Infusion 500 mg
Non-proprietary Name	Lecanemab (Genetical Recombination) (JAN*)
Applicant	Eisai Co., Ltd.
Date of Application	January 16, 2023

Results of Deliberation

In its meeting held on August 21, 2023, the First Committee on New Drugs concluded that the product may be approved and that this result should be presented to the Pharmaceutical Affairs Department of the Pharmaceutical Affairs and Food Sanitation 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 collect information on patient characteristics until data from a specified number of patients are accrued. Furthermore, the applicant should collect data on the safety and efficacy of the product early and take necessary action to ensure the proper use of the product.

**Japanese Accepted Name (modified INN)*

Review Report

August 10, 2023
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	Leqembi for Intravenous Infusion 200 mg Leqembi for Intravenous Infusion 500 mg
Non-proprietary Name	Lecanemab (Genetical Recombination)
Applicant	Eisai Co., Ltd.
Date of Application	January 16, 2023
Dosage Form/Strength	Injection: each vial contains 200 mg or 500 mg of lecanemab (genetical recombination)
Application Classification	Prescription drug, (1) Drug with a new active ingredient
Definition	Lecanemab is a recombinant anti-human amyloid beta peptide monoclonal antibody, the complementarity-determining regions of which are derived from mouse antibody and other regions are derived from human IgG1. Lecanemab is produced in Chinese hamster ovary cells. Lecanemab is a glycoprotein (molecular weight: ca. 150,000) composed of 2 H-chains (γ1-chains) consisting of 454 amino acid residues each and 2 L-chains (κ-chains) consisting of 219 amino acid residues each.

Structure

Light chain (L chain)

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DVVMTQSPLS  LPVTPGAPAS  ISCRSSQSIV  HSNGNTYLEW  YLQKPGQSPK
LLIYKVSNRF  SGVPDRFSGS  GSGTDFTLRI  SRVEAEDVGI  YYCFQGSHVP
PTFGPGTKLE  IKRTVAAPSV  FIFPPSDEQL  KSGTASVVCL  LNNFYPREAK
VQWKVDNALQ  SGNSQESVTE  QDSKDSTYSL  SSTLTLSKAD  YEKHKVYACE
VTHQGLSSPV  TKSFNRGEC
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Heavy chain (H chain)

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EVQLVESGGG  LVQPGGSLRL  SCSASGFTFS  SFGMHWVRQA  PGKGLEWVAY
ISSGSSTIYY  GDTVKGRFTI  SRDNAKNSLF  LQMSSLRAED  TAVYYCAREG
GYYYGRSYYT  MDYWGQGTTV  TVSSASTKGP  SVFPLAPSSK  STSGGTAALG
CLVKDYFPEP  VTVSWNSGAL  TSGVHTFPAV  LQSSGLYSLS  SVVTVPSSSL
GTQTYICNVN  HKPSNTKVDK  RVEPKSCDKT  HTCPPCPAPE  LLGGPSVFLF
PPKPKDTLMI  SRTPEVTCVV  VDVSHEDPEV  KFNWYVDGVE  VHNAKTKPRE
EQYNSTYRVV  SVLTVLHQDW  LNGKEYKCKV  SNKALPAPIE  KTISKAKGQP
REPQVYTLPP  SREEMTKNQV  SLTCLVKGFY  PSDIAVEWES  NGQPENNYKT
TPPVLDSDGS  FFLYSKLTVD  KSRWQQGNVF  SCSVMHEALH  NHYTQKSLSL
SPGK
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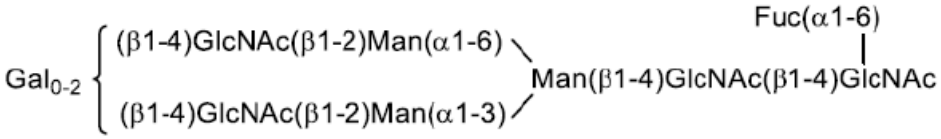
Intra-chain disulfide bonds: shown in solid lines

Inter-chain disulfide bonds: between L-chain C219 and H-chain C227, H-chain C233 and H-chain C233, H-chain C236 and H-chain C236

Partial processing: H-chain K454

Glycosylation: H-chain N304

Deduced structure of major glycan:



Molecular formula: $C_{6544}H_{10088}N_{1744}O_{2032}S_{46}$ (protein moiety, 4 chains)

Molecular weight: 147,179.58

Items Warranting Special Mention

Priority review (PSEHB/PED Notification No. 3, dated January 26, 2023, by the Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare)

Prior assessment consultation conducted

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. The following issues should be further investigated: incidence of amyloid-related imaging abnormality (edema/effusion, cerebral microhemorrhage, superficial siderosis, and cerebral hemorrhage); safety in patients who are taking antiplatelet, anticoagulant, or thrombolytic medication; and long-term safety and efficacy, etc.

Indication

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

Dosage and Administration

The usual dosage is 10 mg/kg of lecanemab (genetical recombination) administered as an intravenous infusion over approximately 1 hour, once every 2 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 collect information on patient characteristics until data from a specified number of patients are accrued. Furthermore, the applicant should collect data on the safety and efficacy of the product early, and take necessary action to ensure the proper use of the product.

Attachment

Review Report (1)

June 16, 2023

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	Leqembi for Intravenous Infusion 200 mg Leqembi for Intravenous Infusion 500 mg
Non-proprietary Name	Lecanemab (Genetical Recombination)
Applicant	Eisai Co., Ltd.
Date of Application	January 16, 2023
Dosage Form/Strength	Injection: each vial contains 200 mg or 500 mg of lecanemab (genetical recombination)

Proposed Indication

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

Proposed Dosage and Administration

The usual dosage is 10 mg/kg of lecanemab (genetical recombination) administered as an intravenous infusion over approximately 1 hour, once every 2 weeks.

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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 gradual progression of overall cognitive decline. It has been shown, among others, that accumulation of amyloid plaques composed of amyloid β (Aβ) outside of neuron cells starts 10 to 20 years before the onset of clinical symptoms. Although the mechanism of the effect of amyloid plaques on AD symptoms has not been elucidated, it has been suggested that accumulation and deposits of Aβ in the brain resulting from an imbalance between production and removal of Aβ causes neurodegeneration, thereby being involved in cognitive decline. Mild cognitive impairment due to Alzheimer's disease (MCI due to AD) is the pre-dementia stage in which patients have pathological AD and mild cognitive impairment but do not have significant difficulty with activities of daily living. In several years, however, the pre-dementia stage can progress to a stage in which cognitive impairment has a significant effect on activities of daily living, and therefore it is considered important to slow the progression of the disease in its early stages including MCI due to AD.

Many different species of Aβ exist in the brain, including monomers, soluble aggregates from small oligomers (dimers and trimers), and larger oligomers, to protofibrils (PFs), and insoluble fibrils. Among the Aβ species, AβPFs are reported to exhibit the strongest neurotoxicity (*Int J Mol Sci.* 2020;21:952). Lecanemab, which was discovered by the applicant, is a recombinant humanized immunoglobulin G1 (IgG1) monoclonal antibody targeting soluble AβPFs. Lecanemab was developed as a drug to slow deterioration of the patient's clinical condition due to disease progression of AD in patients with MCI due to AD and those with mild Alzheimer's disease dementia (AD-D) by selectively binding to soluble AβPFs and removing them by microglial phagocytosis.

The clinical development of lecanemab started in 2010, and since 2017 the applicant has been collaborating with Biogen Inc. in a joint development project. In January 2023, lecanemab was granted accelerated approval for the indication of "treatment of Alzheimer's disease"[1)] in the US based on the data from the global phase II study (Study 201) showing a reduction in Aβ plaques and other effects. Immediately after the accelerated approval, the applicant submitted a partial change application for full approval based on the results of the global phase III study (Study 301), and full approval was granted in June 2023. In Europe, the applicant submitted an application in January 2023. Outside the US, lecanemab is under review in 5 countries and regions including Europe as of June 2023.

In Japan, the clinical development of lecanemab started in 2013. Recently, the applicant filed an application for marketing approval of lecanemab with the proposed indication for "To slow the progression of early Alzheimer's disease (mild cognitive impairment and mild dementia due to Alzheimer's disease)" based on data including results from Study 301, 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"].

[1)] The "Indications and usage" section includes the following statements: treatment with Leqembi should be initiated in patients with early AD, the population in which treatment was initiated in clinical trials; continued approval for this indication may be contingent upon verification of clinical benefit in a confirmatory trial.

In the following sections, unless otherwise specified, “MCI due to AD and mild AD-D” are abbreviated as “early AD” as shown in the Appendix.

2. Quality and Outline of the Review Conducted by PMDA

2.1 Drug substance

2.1.1 Generation and control of cell substrate

Hybridomas were produced by immunizing [redacted] and fusing mouse splenic cells and mouse myeloma cells, and optimal clones were selected based on the binding ability to [redacted] of the antibody to be produced as an indicator. From the clone, the gene sequences encoding the heavy and light chain variable regions are cloned to construct [redacted] chimera expression vector. The sequences of [redacted] and [redacted] were humanized by substituting them with the human sequences. The gene expression construct for lecanemab was created using the gene segments encoding the heavy and light chain variable regions that were [redacted] based on the sequences. The expression construct was introduced into the Chinese hamster ovary (CHO) cell line. The master cell bank (MCB) and working cell bank (WCB) were prepared from a clone optimal for the production of lecanemab.

Characterization and purity tests of MCB, WCB, and extend end of production cell bank (EEPCB) were performed 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. 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: thawing of WCB, seed culture, production culture, harvesting, viral inactivation ([redacted]), [redacted] chromatography, viral inactivation ([redacted]), [redacted] chromatography, [redacted] chromatography, virus removal filtration, [redacted], [redacted], [redacted] final filtration, and storage/testing.

Critical steps are [redacted], [redacted], [redacted], [redacted], [redacted], [redacted], [redacted], [redacted], [redacted], [redacted], [redacted], [redacted], and [redacted].

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

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 EEPCB [see Section "2.1.1 Generation and control of cell substrate"]. Bioburden testing, mycoplasma testing, and *in vitro* adventitious 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 infectious substances. These tests on pre-harvest unprocessed bulk are selected as in-process control tests.

A viral clearance study was performed with model viruses for the purification process. The results showed 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})			
	Xenotropic murine leukemia virus	Minute virus of mice	Pseudorabies virus	Reovirus type 3
Viral inactivation ( )				
Viral inactivation ( )				
chromatography				
chromatography				
Viral removal filtration				
Overall virus reduction factor	≥21.94	≥10.43	≥20.59	≥9.77

2.1.4 Manufacturing process development (comparability)

The major changes made to the manufacturing process during the drug substance development process are shown below (the manufacturing processes are referred to, in the order of development, as Process A, Process B, Process C, and the proposed manufacturing process). The formulations manufactured using the drug substances of , , and were used in Phase I, II, and III studies, respectively.

- From Process A to Process B: changes in , , , and , as well as
- From Process B to Process C: changes in , , and , as well as
- From Process C to the proposed manufacturing process: changes in and

When the manufacturing processes were changed, comparability was evaluated in terms of quality attributes. The results demonstrated comparability of the drug substance before and after the change.

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, molecular weight, post-translational modifications ([redacted], [redacted], and [redacted]), [redacted], disulfide bonds, trisulfide bonds, free thiol group, secondary structure, tertiary structure, thermal stability
Physicochemical properties	Size variants, charge variants
Glycan structure	N-linked glycan profile, sialic acid
Biological properties	Aβ binding activity
	Binding affinity for [redacted], ([redacted], [redacted], and [redacted]), binding affinity for [redacted]
	ADCP activity

Main evaluation results for biological properties were as follows:

- The Aβ binding activity was measured by [redacted]. The results demonstrated the binding ability of lecanemab to Aβ.
- Binding affinity for [redacted] and that for [redacted] were measured by [redacted]. The results demonstrated the binding ability of lecanemab to [redacted] and [redacted].
- Antibody dependent cellular phagocytosis (ADCP) activity was measured by [redacted] using [redacted], and the results demonstrated that lecanemab has ADCP activity.

2.1.5.2 Product-related substances/Product-related impurities

On the basis of the results of characterization studies in Section 2.1.5.1 and other data, [redacted], [redacted], [redacted], [redacted], and [redacted] were identified as product-related substances. Impurity A, Impurity B, and Impurity C were identified as product-related impurities, which are adequately controlled by the specifications for the drug substance and drug product.

2.1.5.3 Process-related impurities

Host cell proteins (HCPs), host cell deoxyribonucleic acid (DNA), Impurity D, Impurity E, Impurity F, Impurity G, Impurity H, bacterial endotoxins, and bioburden were defined as process-related impurities. It has been verified that all the process-related impurities are adequately removed in the manufacturing process. Impurity I, Impurity J, Impurity D, and bioburden are controlled by the specifications for the drug substance, while bacterial endotoxins are controlled by the specifications for the drug substance and those of the drug product.

2.1.6 Control of drug substance

The proposed specifications for the drug substance include content, description, identification ([redacted]), glycan profiles, osmolality, pH, purity (capillary electrophoresis-sodium dodecyl sulfate [CE-SDS; non-reducing and reducing conditions], size exclusion liquid chromatography [SEC], [redacted] chromatography [[redacted]C], Impurity J, Impurity I, and Impurity D), bacterial endotoxins, microbial limit, [redacted], biological activity ([redacted] and [redacted]), 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	Number of batches	Storage condition	Study period	Storage form
Long-term	Process C	3	± °C	months[a]	plastic bag
	Proposed process	4		months[a]	
Accelerated	Process C	3	± °C	months	
	Proposed process	4		months	
Stress	Process C	3	± °C / ± % RH	months	
	Proposed process	4		months	

a, The stability testing is ongoing up to months

The long-term test showed no clear changes in quality attributes throughout the testing period.

The accelerated testing showed a trend towards an increase in , , and .

The stress testing showed an increase in , , , , , and , and a trend toward a decrease in and .

On the basis of the above, a shelf life of months has been proposed for the drug substance when stored at ≤ in a plastic bag.

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 (10 mL), containing 200 mg/2 mL of lecanemab or 500 mg/5 mL of lecanemab. The drug product contains, as excipients, L-histidine, L-histidine hydrochloride hydrate, L-arginine hydrochloride, polysorbate 80, and water for injection.

2.2.2 Manufacturing process

The manufacturing process for the drug product consists of , , , , bioburden reducing filtration, sterile filtration, filling/stoppering/crimping, sorting, packaging/labeling/storage, and testing.

Critical steps are and .

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

2.2.3 Manufacturing process development

The major changes to the manufacturing process during the development of the drug product are shown below. These changes in the manufacturing process were made at the same time as each change was made to the manufacturing process of the drug substance [see Section “2.1.4 Manufacturing process development

(comparability)"] (based on the names of the manufacturing processes for the drug substances, the manufacturing processes for the drug product are designated, in the order of development, as Process A-1, Process A-2, Process B, Process C, and the proposed manufacturing process). The formulations used in the studies were as follows: [redacted] in the phase I study, [redacted] in the phase II study, and [redacted] in the phase III study.

- From Process A-1 to Process A-2: a change in [redacted]
- From Process A to Process B: changes in [redacted], prescription, and [redacted]
- From Process B to Process C: changes in [redacted] and prescription, as well as [redacted]
- From Process C to the proposed manufacturing process: changes in [redacted] and [redacted]

When the manufacturing processes were changed, comparability was evaluated in terms of quality attributes. The results demonstrated comparability of the drug product before and after the change.

2.2.4 Control of drug product

The proposed specifications for the drug product include strength, description, identification ([redacted]), osmolality, pH, purity (CE-SDS [non-reducing and reducing conditions], SEC, and [redacted]C), bacterial endotoxins, extractable volume, foreign insoluble matter, insoluble particulate matter, sterility, [redacted], biological activity ([redacted] and [redacted]), 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

	Specification	Manufacturing process	Number of batches	Storage condition	Study period	Storage form
Long-term	200 mg	Process C	3	5 ± 3°C	18 months[a]	Glass vial and [redacted] rubber stopper
	500 mg		3			
	200 mg	Proposed process	3		[redacted] months[a]	
	500 mg		4			
Accelerated	200 mg	Process C	3	25 ± 2°C/ 60 ± 5% RH	6 months	
	500 mg		3			
	200 mg	Proposed process	3		6 months	
	500 mg		4			
Stress	200 mg	Process C	3	40 ± 2°C/ 75 ± 5% RH	6 months	
	500 mg		3			
	200 mg	Proposed process	3		6 months	
	500 mg		4			
Photostability	200 mg	Process C	1	Overall illumination of ≥1.2 million lux·h and an integrated near ultraviolet energy of ≥200 W·h/m^2 at 25°C/60%RH		
	500 mg		1			

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

The long-term test showed a trend toward an increase in [redacted] and a trend toward a decrease in [redacted]. For other parameters, however, no clear changes in quality attributes were observed throughout the period of the long-term testing.

The accelerated testing showed an increase in [redacted], a trend toward an increase in [redacted], and a trend toward a decrease in [redacted] and [redacted].

The stress testing showed increases in [redacted] and [redacted], and decreases in [redacted], [redacted], and [redacted].

Photostability testing showed that the drug product is photolabile.

On the basis of the above, a shelf life of 18 months was proposed for both formulations when placed in the primary container of glass vial and [redacted] rubber stopper 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 including the following, a method to control quality attributes of the drug product through a combination of process parameter control, in-process parameter testing, and specifications was developed [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"].

- Identification of critical quality attributes (CQAs):

The following CQAs were identified based on the information obtained through the development of the drug product and related findings.

CQAs for the drug substance:	description (color and clarity), pH, osmolality, [redacted], identification ([redacted]), protein concentration, purity by CE-SDS (non-reducing and reducing conditions), [redacted], Impurity A, Impurity B, and Impurity K, [redacted], HCP, host cell DNA, Impurity G, microbial contamination (bioburden and sterility), bacterial endotoxins, and adventitious infectious substances
CQAs for the drug product:	description (visible particles), extractable volume, insoluble particulate matter (≥10 μm and ≥25 μm ranges)

- Process characterization:

The process risk assessment and characterization allowed to investigate the operational range of process parameters and to identify process parameters that have impacts on CQAs and process performance.

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 characteristics and selectivity of lecanemab for Aβ (CTD 4.2.1.1.38, 4.2.1.1.39, 4.2.1.1.1 [reference data], and 4.2.1.1.4 [reference data])

The geometric mean [95% confidence interval (CI)] of Aβ (1-40) monomer and Aβ (1-42) PF concentrations required to reduce the concentration of free lecanemab by 50% as measured by enzyme-linked immunosorbent assay (ELISA) were 27000 nmol/L [95% CI: 13000, 57000] and 3.6 nmol/L [95% CI: 2.7, 4.8], respectively.

A surface plasmon resonance (SPR)[2)] assay was performed to determine the equilibrium constant (K_D) to evaluate the binding affinity of lecanemab for the Aβ species. The binding of lecanemab to Aβ (1-40) monomer and Aβ (1-42) PF, reported as K_D or K_{D1} (geometric mean), was 1700 nmol/L and 1.16 nmol/L, respectively.

The mean concentrations of Aβ (1-40) monomer, small Aβ (1-42) PFs,[3)] and large Aβ (1-42) PFs[4)] that were required to reduce the concentration of free lecanemab by 50% as measured by ELISA were >25000, 0.80, and 0.79 nmol/L, respectively. Similarly, crosslinked Aβ (1-42) PF and crosslinked Aβ (1-42) oligomers (dimer to trimer, hexamer to octamer, and octamer to dodecamer) prepared by incubating and photo-crosslinking an Aβ (1-42) monomer were evaluated. The mean concentrations required to reduce the concentration of free lecanemab by 50% were 1.04, >436.5, >40.89, and 6.09 nmol/L, respectively. In a study of Aβ (pE3-42) PF, a modified Aβ which is considered to promote aggregation of Aβ, lecanemab did not bind to Aβ (pE3-42) PF.

The binding affinity (reported as mean K_D or K_{D1}) of lecanemab for Aβ (1-28) monomer, small Aβ (1-42) PF,[3)] large Aβ (1-42) PF,[4)] Aβ (1-40) fibril, and Aβ (1-42) fibril as determined by SPR assay[5)] was 2290, 0.97, 0.16, 1.33, and 1.79 nmol/L, respectively. Similarly, crosslinked Aβ (1-42) oligomers were evaluated. The binding affinity (mean K_{D1}) of lecanemab to non-crosslinked Aβ (1-42) PF, crosslinked Aβ (1-42) PF, and crosslinked Aβ (1-42) oligomers (dimer to trimer, hexamer to octamer, and octamer to dodecamer) was 1.92, 3.02, 270, 67.3, and 29.1 nmol/L, respectively. In a study of Aβ (pE3-42) PF, the K_{D1} (mean) was 232 nmol/L.

Soluble brain extracts prepared from fresh frozen temporal cortex tissue of 3 patients who had been diagnosed as having AD and homozygous for the *APOE4* allele were incubated with lecanemab (0.068–68000 pmol/L), and then the levels of Aβ bound to lecanemab were quantified by electrochemiluminescence immunoassay (ECLIA). Amyloid β protofibrils in the supernatant were detected using mAb158, the murine IgG2a

2) The Aβ (1-40) monomer was analyzed with a 1:1 binding model while Aβ (1-42) PF was analyzed with a bivalent analyte model.
3) The estimated size is 75 to 400 kDa
4) The estimated size is 300 to 5000 kDa
5) The Aβ (1-28) monomer was analyzed with a 1:1 binding model, while other Aβ species were analyzed with a bivalent analyte model. K_{D2} values are not shown because the bivalent analyte model used was not able to determine accurate K_{D2} values.

homologous antibody of lecanemab. The results showed that AβPF levels in the supernatant decreased in a manner dependent on the concentration of lecanemab. Immunoprecipitated Aβ (x-40) and Aβ (x-42) increased in a manner dependent on the concentration of lecanemab. The 50% effective concentration (EC_{50}) for Aβ (x-42) was lower than the EC_{50} for Aβ (x-40).

3.1.1.2 Binding characteristics and selectivity of lecanemab and mAb158 for Aβ (CTD 4.2.1.1.2 [reference data], 4.2.1.1.3 [reference data], and 4.2.1.1.6 [reference data])

The concentrations of Aβ (1-40) monomer and AβPF required to reduce the concentration of free lecanemab or mAb158[6)] by 50% as measured by ELISA were 3300 and 3.3 nmol/L, respectively for lecanemab, and 6000 and 5 nmol/L, respectively, for mAb158.

The binding capacity of mAb158 to Aβ (1-42) PF (46-mer) and Aβ (1-42) oligomers (trimer and hexamer) were evaluated by measuring the quantity of each bound Aβ species by ELISA. The binding capacity was the highest for Aβ (1-42) PF (46-mer), followed by, in the descending order, Aβ (1-42) oligomer (hexamer) and Aβ (1-42) oligomer (trimer).

The association rate constant (k_a), dissociation rate constant (k_d), and K_D, of lecanemab or mAb158 for Aβ (1-40) monomer and Aβ (1-42) PF were investigated by SPR.[7)] The K_D values for binding to Aβ monomer were 3300 nmol/L (lecanemab) and 4200 nmol/L (mAb158). The k_{a1} values for binding to AβPF were 6.6×10^5 $L \cdot mol^{-1} \cdot s^{-1}$ (lecanemab) and 5.1×10^5 $L \cdot mol^{-1} \cdot s^{-1}$ (mAb158), while the k_{d1} values for binding to AβPF were 0.0013 s^{-1} (lecanemab) and 0.0032 s^{-1} (mAb158).

To evaluate the binding capacity of lecanemab (0.0008–5 nmol/L), F (ab')$_2$-2401, a binding fragment of lecanemab (0.0008–5 nmol/L), mAb158 (1.3 nmol/L), and Fab158, a binding fragment of mAb158 (2, 20, and 200 nmol/L) to AβPF, the amount of each binding fragment bound to AβPF was measured by ELISA. The binding capacity of lecanemab to AβPF was similar to that of F (ab')$_2$-2401 to AβPF, and the binding capacity of Fab158 to AβPF was lower than that of mAb158 to AβPF.

3.1.1.3 The binding site for lecanemab on Aβ and structure of lecanemab–Aβ complex (CTD 4.2.1.1.5 [reference data], 4.2.1.1.7 [reference data], and 4.2.1.1.41 [reference data])

The binding sites to lecanemab on Aβ were investigated by biolayer interferometry (BLI) using six C-terminal biotinylated peptides, i.e., Aβ (1-16), Aβ (2-16), Aβ (3-16), Aβ (4-16), Aβ (5-16), or Aβ (6-16), and two N-terminal biotinylated peptides, i.e., Aβ (1-16) or Aβ (1-42). The results of the BLI analysis showed that lecanemab had high affinity for C-terminal biotinylated Aβ (1-16) and Aβ (2-16) peptides and partial affinity for C-terminal biotinylated Aβ (3-16); however, lecanemab did not show affinity for other C-terminal

6) Since lecanemab is a humanized antibody, there was a concern that following its administration to mice, anti-drug antibodies would be produced, preventing the antibody concentrations from reaching an adequate level for efficacy evaluation. Therefore, the main pharmacology studies in mice used mAb158, the murine IgG2a homologous antibody of lecanemab.

7) The Aβ monomer was analyzed with a 1:1 binding model, while AβPF was analyzed with a bivalent analyte model. Because the bivalent analyte model studied was not able to determine accurate k_{a2} and K_{d2} values, these values are not shown here.

biotinylated peptides or N-terminal biotinylated peptides, suggesting that 2 to 3 amino acid residues from the N-terminal region of Aβ play key roles in the binding of lecanemab.

The antigen-binding fragment (Fab) of lecanemab in complex with the Aβ (1-9) peptide was analyzed by X-ray structural analysis. The results showed that the 2 Fabs were forming an asymmetric unit, and the Aβ (1-9) peptide binds to one of the two Fabs.

The hydrogen/deuterium (H/D) exchange for Aβ (1-40) monomer and Aβ (1-42) PF in a phosphate-buffered saline (PBS) solution in the presence and absence of lecanemab was investigated by hydrogen-deuterium exchange mass spectrometry. In the absence of lecanemab, H/D exchange was observed in the N-terminal region (1-19) and mid-region (20-34) for both Aβ (1-40) monomer and Aβ (1-42) PF, while in the presence of lecanemab, decreased H/D exchange was observed in the N-terminal region of Aβ (1-40) monomer and in the N-terminal region and mid-region of Aβ (1-42) PF. Based on the above, the applicant discussed the following possibilities: (1) lecanemab may interact with a conformational epitope consisting of both the N-terminal region and mid-region of Aβ (1-42) PF; or (2) lecanemab may cause structural change of the mid-region by binding to the N-terminal region of Aβ (1-42) PF.

3.1.1.4 Inhibition of β sheet formation of Aβ by lecanemab and mAb158 (CTD 4.2.1.1.8 [reference data])

Lecanemab (680 nmol/L), mAb158 (670 nmol/L), human IgG1 control antibody (100 μg/mL), mouse IgG2a control antibody (100 μg/mL), or vehicle (PBS) was incubated in the presence of Aβ (1-42) oligomer and thioflavin T to investigate β sheet formation by time-course measurement of fluorescence intensity. The fluorescence intensity increased over time in human IgG1, mouse IgG2a, and vehicle while fluorescence intensity did not increase in lecanemab and mAb158.

3.1.1.5 Inhibition of AβPF binding to rat hippocampal neurons by lecanemab or mAb158 (CTD 4.2.1.1.9 [reference data], and 4.2.1.1.10)

Using the primary culture of fetal rat hippocampal neurons, lecanemab (0.02–680 nmol/L), human IgG control antibody (100 μg/mL), or vehicle (PBS) was added together with Aβ (1-42) PF, and incubated. The amount of AβPFs bound to dendritic spines was measured by immunofluorescence. Lecanemab inhibited AβPF binding to dendritic spines in a concentration-dependent manner and the mean concentration causing a 50% reduction (IC_{50}) in binding was 8.2 nmol/L [95% CI: 2.3, 30]. In the analysis of mAb158 (67 nmol/L), mAb158 completely inhibited AβPF binding to dendritic spines.[8)]

3.1.1.6 The effect of lecanemab on Aβ-induced cytotoxicity (CTD 4.2.1.1.11 [reference data], 4.2.1.1.12 [reference data], and 4.2.1.1.13 [reference data])

Amyloid β (1-42) aggregates (0, 1000 nmol/L) were incubated with lecanemab (0, 10, 30, 100, 300, 1000, and 3000 nmol/L), added to the primary culture of chicken fetal cerebral cortex neurons or SH-SY5Y cells, cultured

[8)] The area coimmunostained with anti-PSD-95 antibody and anti-Aβ antibody was 0 ± 0% (mean ± standard error).

for 144 hours and 96 hours, respectively, and evaluated for cell viability by the MTT assay. The cell viability for the primary neuron culture in the presence of Aβ (1-42) aggregates was approximately 60% of that in the absence of Aβ (1-42) aggregates. The cell viability tended to increase in a manner dependent on the concentration of lecanemab, with a viability of approximately 80% at 3000 nmol/L of lecanemab. The cell viability for SH-SY5Y cells in the presence of Aβ (1-42) aggregates was approximately 60% of that in the absence of Aβ (1-42) aggregates. The maximum viability of 74% was achieved when 100 nmol/L of lecanemab was added.

After the primary neuron culture from the septal area of fetal rat was incubated in the presence of lecanemab (680 and 2000 nmol/L), mAb158 (670 nmol/L), or vehicle (PBS), Aβ (1-42) PF was added, and the percentage[9)] of lactate dehydrogenase (LDH) released into the extracellular space at 2 days after culture was measured. The mean percentage of LDH released due to addition of Aβ (1-42) PF was 13.3% (lecanemab 680 nmol/L) and 9.5% (lecanemab 2000 nmol/L), 10.7% (mAb158 670 nmol/L), and 21.4% (vehicle), indicating lower LDH release with lecanemab and mAb158 compared with the vehicle. Similarly, the percentage of LDH released due to addition of Aβ (1-42) oligomer was also investigated in terms of the effect of lecanemab (136, 272, 408, 544, or 680 nmol/L) or mAb158 (670 nmol/L). The mean percentage of LDH released was 8.8% to 16.9% (lecanemab 136–680 nmol/L) and 16.3% (vehicle), indicating lower LDH release at lecanemab ≥272 nmol/L compared with the vehicle. The results for mAb158 at 670 nmol/L (19.3%) did not differ from vehicle (22.0%).

In another study, after the primary neuron culture from the septal area of fetal rat was incubated in the presence of lecanemab (340, 1020, 5100, or 6800 nmol/L) or vehicle (PBS), Aβ (1-42) PF was added, and the percentage of LDH released into the extracellular space at 2 days after culture was measured. The mean percentage of LDH released for cultures treated with lecanemab (10.9%–12.4%) did not differ from that for cultures treated with vehicle (11.6%).

3.1.1.7 The effect of lecanemab on Aβ-induced long-term potentiation (LTP) impairment using mouse hippocampus (CTD 4.2.1.1.14 [reference data])

Mixtures of lecanemab (2 and 20 nmol/L) and Aβ (1-42) (mainly oligomers; 1000 nmol/L), Aβ (1-42) (mainly oligomers; 1000 nmol/L), or vehicle added to artificial cerebrospinal fluid (CSF) were allowed to react with mouse hippocampal slices (4–7 slices/group) for 15 minutes. Then theta burst stimulation was applied (100 Hz; 15 electrical stimulations of 4 pulses at 5 Hz intervals) to induce long-term potentiation (LTP), and field excitatory postsynaptic potentials 90 minutes after theta burst stimulation was evaluated. The mean percent change from baseline in field excitatory postsynaptic potential 90 minutes after theta burst stimulation was as follows: +62.8% in the vehicle group and +18.3% in the Aβ (1-42) group, indicating a significantly smaller change in the Aβ (1-42) group than in the vehicle group; and +36.8% and +47.4% in the lecanemab 2 and 20 nmol/L groups, respectively, indicating a significantly greater change in the 20 nmol/L group than in the Aβ (1-42) group.

9) The percentage of LDH activity in culture to the total LDH activity in cells and culture.

3.1.1.8 Binding affinity for Fc receptor (FcR) (CTD 4.2.1.1.15 [reference data], 4.2.1.1.16 [reference data], 4.2.1.1.17 [reference data])

The binding affinity of lecanemab and mAb158 for human or mouse Fcγ receptor (FcγR) I was investigated by ELISA. While the binding affinity of mAb158 for mouse FcγRI was 16 times that of lecanemab for mouse FcγRI, the binding affinity of lecanemab for human FcγRI was similar to that of mAb158 for human FcγRI.

The binding affinity (K_D) of lecanemab and mAb158 for human or mouse FcγRI was measured by SPR. The mean K_D of lecanemab was 19 and 220 nmol/L for human and mouse FcγRI, respectively, and the mean K_D of mAb158 was 31 and 19 nmol/L for human and mouse FcγRI, respectively.

His-tagged human recombinant Fc protein was immobilized on the sensor, and the binding affinity for human FcγR was investigated by BLI using lecanemab (25 and 50 μg/mL), human IgG (25 and 50 μg/mL), or Control Antibody A (25 and 50 μg/mL), which has the same Fc as lecanemab. The results showed that the K_D for binding to FcγRI was 8.56 and 7.33 nmol/L for lecanemab at 25 and 50 μg/mL, respectively, 18.3 and 31.8 nmol/L for human IgG at 25 and 50 μg/mL, respectively, and 8.13 and 7.37 nmol/L for Control Antibody A at 25 and 50 μg/mL, respectively. Lecanemab did not exhibit binding affinity for FcγRII b/c. The binding affinity (K_D) for FcγRIII a/b was 49.9 and 42.1 nmol/L for lecanemab at 25 and 50 μg/mL, respectively, 23.3 and 19.5 nmol/L for human IgG at 25 and 50 μg/mL, respectively, and 39.8 and 31.1 nmol/L for Control Antibody A at 25 and 50 μg/mL, respectively.

The binding affinity (K_D) of lecanemab for human neonatal Fc receptor (FcRn) was measured by SPR. The K_D was 0.64 μmol/L at pH 6, and at pH 7.4, specific but low binding affinity was observed.

3.1.1.9 Effects on microglial removal of Aβ (CTD 4.2.1.1.18 [reference data] and 4.2.1.1.19 [reference data])

The Aβ (1-42) PF (100 nmol/L)–lecanemab (0.04-10 μg/mL) complex was added to EOC 20 cells in the presence or absence of FcγR inhibitor. After incubating the cells for 2 hours, the level of intracellular AβPF was measured by ELISA. Lecanemab increased AβPF uptake in EOC 20 cells in a concentration-dependent manner in the absence of FcγR inhibitor, and the EC_{50} (mean ± standard deviation) of FcR-mediated AβPF uptake for lecanemab was 257 ± 61 ng/mL. In the presence of FcγR inhibitor, the AβPF uptake in EOC 20 cells decreased in a manner dependent on lecanemab concentration. The level of AβPF uptake obtained by subtracting AβPF uptake in the presence of FcγR inhibitor from that in the absence of FcγR inhibitor was close to the level of AβPF uptake in the absence of FcγR inhibitor in a manner dependent on the concentration of lecanemab.

After AβPF (1 ng/mL) and an equimolar quantity of lecanemab or vehicle were added to microglia from patients with AD in the presence or absence of FcR inhibitor, and incubated for 12 hours, the intracellular AβPF levels were measured by ELISA. The intracellular AβPF concentrations (mean ± standard error) when only AβPF was added to microglia were 79.75 ± 5.15 and 98.23 ± 8.12 pg/mL in the presence and absence of

FcR inhibitor, respectively. The intracellular AβPF concentrations (mean ± standard error) when AβPFs and lecanemab were added to microglia were 17.78 ± 5.89 and 164.50 ± 12.28 pg/mL in the presence and absence of FcR inhibitor, respectively.

3.1.2 *In vivo* studies

3.1.2.1 Effects of mAb158 on the brain levels of AβPF in APP^{NL-G-F} mice (CTD 4.2.1.1.43)

To 6-month-old male amyloid precursor protein $(APP)^{NL-G-F}$ mice[10] (N = 8-10/group), mAb158 (10 or 30 mg/kg) or vehicle (PBS) was administered once weekly intraperitoneally for 16 weeks. Brains were harvested 7 days after the final dose, and the levels of various species of Aβ in the brain were measured by ELISA. The plaque area in the whole brain except for the olfactory bulb and brain ventricle was quantified by immunohistochemistry staining with anti-human Aβ N-terminus monoclonal antibody 82E1. The results (mean ± standard error) were as follows: the brain levels of AβPF were 7.44 ± 0.88 pmol/g (mAb158 10 mg/kg), 7.55 ± 1.06 pmol/g (mAb158 30 mg/kg), and 15.11 ± 0.92 pmol/g (vehicle); levels of soluble Aβ (1-42) were 35.2 ± 1.8 pmol/g (mAb158 10 mg/kg), 33.2 ± 1.8 pmol/g (mAb158 30 mg/kg), and 127.5 ± 12.4 pmol/g (vehicle); and levels of insoluble Aβ (1-42) were 959 ± 48 pmol/g (mAb158 10 mg/kg), 1240 ± 53 pmol/g (mAb158 30 mg/kg), and 2884 ± 72 pmol/g (vehicle), indicating that the levels were significantly lower in the mAb158 10 and 30 mg/kg groups than in the vehicle group for all Aβ measurements. The Aβ plaque area was significantly smaller at both dosages of mAb158 than the vehicle.

3.1.2.2 Effects of mAb158 on the brain levels of AβPF in transgenic (Tg) 2576 mice (CTD 4.2.1.1.27 [reference data], 4.2.1.1.29 [reference data], 4.2.1.1.30 [reference data], 4.2.1.1.31 [reference data], 4.2.1.1.32 [reference data], 4.2.1.1.33 [reference data], and 4.2.1.1.42 [reference data])

To 12-month-old female Tg2576 mice[11] (N = 11-17/group), mAb158 (35 mg/kg) or vehicle (PBS) was administered once weekly intraperitoneally for 4 or 18 weeks. Brains were harvested 7 days after the final dose, and the levels of various Aβ species in the brain were measured by ECLIA. Amyloid β plaques and dense core plaques in the cerebral cortex were quantified by immunohistochemistry staining with anti-human Aβ (1-16) monoclonal antibody 6E10 and by thioflavin S staining. The brain levels of AβPF (mean ± standard deviation; the same shall apply hereinafter in this section) were 4.9 ± 3.1 ng/g (mAb158) and 13.0 ± 6.5 ng/g (vehicle) at Week 4, and 13.1 ± 7.7 ng/g (mAb158) and 103.2 ± 52.5 ng/g (vehicle) at Week 18, indicating that the level of AβPF was significantly lower in the mAb158 group than in the vehicle group at both timepoints. The brain levels of soluble and insoluble Aβ (x-42) at Week 18 were significantly lower in the mAb158 group than in the vehicle group; in contrast, there were no between-group differences in the brain levels of soluble and insoluble Aβ (x-38) or in the brain levels of soluble and insoluble Aβ (x-40). At Week 4, there were no differences between the groups in the brain levels of each Aβ species. The Aβ plaque area and Aβ plaque density in the cerebral cortex were significantly lower in the mAb158 group than in the vehicle group at Week 18. At Week 4, there were no differences between the groups in Aβ plaque area and density. Both at Weeks 4

[10] A mouse model of AD that contains a knocked-in human *APP* gene harboring the Swedish mutation (K670N/M671L), Arctic mutation (E693G), and Iberian mutation (I716F), developing Aβ plaques before reaching 6 months of age.
[11] A mouse model of AD that overexpresses human *APP* gene harboring the Swedish mutation (K670N/M671L), developing Aβ plaques around 9 to 12 months of age.

and 18, there were no differences in the area of dense core plaques area and density in the cerebral cortex between the groups.

To 12-month-old female Tg2576 mice (N = 15-18/group), mAb158 (1, 5, 15, or 50 mg/kg) or vehicle (PBS) was administered once weekly intraperitoneally for 18 weeks. Brains were harvested 5 days after the final dose, and the levels of various Aβ species in the brain were measured by ELISA. The areas of Aβ plaques and dense core plaques in the cerebral cortex and hippocampus were quantified by immunohistochemistry staining with anti-human Aβ (1-16) monoclonal antibody 6E10, anti-Aβ40 antibody, and anti-Aβ42 antibody and by thioflavin S staining. The brain levels of AβPF were 4481 ± 803, 5467 ± 1055, 3528 ± 714, and 1170 ± 309 pmol/L, respectively, at the mAb158 dose levels of 1, 5, 15, and 50 mg/kg, and 4593 ± 931 pmol/L in the vehicle group, indicating that the brain levels of AβPF were significantly lower in the mAb158 50 mg/kg group than in the vehicle group. The level of soluble Aβ (1-42) was significantly lower in the mAb158 50 mg/kg group than in the vehicle group. The levels of soluble Aβ (x-40), insoluble Aβ (1-40), and insoluble Aβ (x-40) were significantly higher in the mAb158 5 mg/kg group than in the vehicle group. At other dose levels of mAb158, there were no differences in the levels of insoluble Aβ (1-40), Aβ (x-40), and Aβ (1-42), and Aβ (x-42) between the mAb158 and vehicle groups. The Aβ plaque and dense core plaque areas in the cerebral cortex and hippocampus in all the dose groups of mAb158 did not differ from those of the vehicle group.

To 20-month-old female Tg2576 mice (N = 18-34/group), mAb158 (24 mg/kg) or vehicle (PBS) was administered once weekly intraperitoneally for 4 weeks. Brains were harvested 24 hours after the final dose, and the levels of various Aβ species in the brain were measured by ELISA. The brain levels of AβPF were 15.8 ± 2.0 and 22.2 ± 4.0 nmol/L in the mAb158 and vehicle groups, respectively, indicating no difference between the groups. There were no differences in the levels of soluble or insoluble Aβ (1-40), Aβ (1-42), Aβ (x-40), and Aβ (x-42) between the groups.

To 4-month-old female Tg2576 mice (N = 14-15/group), mAb158 (3, 6, and 12 mg/kg) or vehicle (PBS) was administered once weekly intraperitoneally for 18 weeks. Brains were harvested and CSF was collected 5 days after the final dose, and the brain levels and CSF levels of Aβ (1-42) PF were measured by ELISA. The brain levels of AβPF were 1.02 ± 0.04, 1.00 ± 0.04, and 0.98 ± 0.05 optical density (OD) at 450 nm, respectively, at the mAb158 dose levels of 3, 6, and 12 mg/kg, and 1.18 ± 0.04 OD (450 nm) in the vehicle group, indicating that the levels were significantly lower in all the dose groups of mAb158 than in the vehicle group. The CSF levels of AβPF were 51 ± 8, 37 ± 15, and 24 ± 7 pmol/L, respectively, at the mAb158 dose levels of 3, 6, and 12 mg/kg, and 46 ± 6 pmol/L in the vehicle group, indicating that there was no between-group difference.

To 12.5-month-old female Tg2576 mice (N = 20/group), mAb158 12 or 24 mg/kg, control antibody (IgG) 24 mg/kg, or vehicle (PBS) was administered once weekly intraperitoneally for 18 weeks. Brains were harvested 5 days after the final dose. The areas of Aβ plaques and dense core plaques in the cerebral cortex and hippocampus were quantified by immunohistochemistry staining with anti-human Aβ (1-16) monoclonal antibody 6E10 and by thioflavin S staining. At all dose levels of mAb158, the Aβ plaque area in the cerebral cortex was significantly lower than that in the control antibody group and the vehicle group. In the hippocampus,

the Aβ plaque area was significantly lower than the control antibody group at all dose levels of mAb158; however, the area did not differ from the vehicle group. Both in the cerebral cortex and hippocampus, the area of dense core plaques in all the dose groups of mAb158 did not differ from that of the control antibody group or the vehicle group.

To 10-month-old female Tg2576 mice and wild-type littermates (N = 15-20/group), mAb158 50 mg/kg or vehicle (PBS) was administered once weekly intraperitoneally for 12 weeks. Brains were harvested 7 or 8 days after the final dose, and the areas of Aβ plaques were quantified by immunohistochemistry staining with anti-human Aβ (1-16) monoclonal antibody 6E10 and anti-human Aβ (17-24) monoclonal antibody p2454. Microglia were stained by immunohistochemistry using anti-Iba1 antibody, and microglia without protrusion was quantified as activated microglia. In Tg2576 mice, the area for 6E10-positive Aβ plaques in the hippocampus was significantly smaller in the mAb158 group than in the vehicle group, while in the cerebral cortex, there were no differences between the groups. The area for p2454-positive Aβ plaques was significantly smaller in the mAb158 group than in the vehicle group both in the cerebral cortex and in the hippocampus. In the hippocampus, the number of activated microglia was significantly lower in the mAb158 group than in the vehicle group, while in the cerebral cortex, there was no difference between the groups.

To 12-month-old female Tg2576 mice (N = 18-21/group), mAb158 35 mg/kg or vehicle (PBS) was administered once weekly intraperitoneally for 18 weeks. Brains were harvested 7 days or 12 weeks after the final dose, and the levels of various Aβ species in the brain were measured by ECLIA. Amyloid β plaques and dense core plaques in the cerebral cortex were quantified by immunohistochemistry staining with anti-human Aβ monoclonal antibody 6E10 and by thioflavin S staining. The brain levels of AβPF were 22.5 ± 3.6 ng/g (Day 7) and 45.2 ± 17.2 ng/g (Week 12) in the mAb158 group and 163.6 ± 81.8 ng/g (Day 7) and 328.8 ± 101.9 ng/g (Week 12) in the vehicle group, indicating that the AβPF levels were significantly lower in the mAb158 group than in the vehicle group at both timepoints. The levels of soluble and insoluble Aβ (x-42) were significantly lower in the mAb158 group than in the vehicle group at both timepoints. There were no differences between the groups in the levels of soluble and insoluble Aβ (x-38) and Aβ (x-40). The area and density of Aβ plaques were significantly lower in the mAb158 group than in the vehicle group at both timepoints. There were no differences in the area and density of dense core plaques between the groups at both timepoints.

3.1.2.3 Effects of mAb158 on AβPF in Tg-APP$_{ArcSwe}$ mice (CTD 4.2.1.1.22 [reference data], 4.2.1.1.23 [reference data], 4.2.1.1.24 [reference data], 4.2.1.1.25 [reference data], and 4.2.1.1.26 [reference data])

To 9- to 16- month-old male and female Tg-APP$_{ArcSwe}$ mice[12)] (N = 6/group), mAb158 (1, 3, or 10 mg/kg) or vehicle (PBS) was administered once weekly intraperitoneally for 4 weeks. Brains were harvested 7 days after the final dose, and the brain levels of AβPF were measured by ELISA. The brain levels of AβPF (mean ± standard error) were 470.9 ± 133.2, 256.6 ± 36.1, and 193.3 ± 56.6 pmol/L, respectively, at the mAb158 dose

12) A mouse model of AD that overexpresses human *APP* gene harboring the Swedish mutation (K670N/M671L) and Arctic mutation (E693G), developing Aβ plaques around 5 to 6 months of age.

levels of 1, 3, and 10 mg/kg, and 631.1 ± 152.0 pmol/L in the vehicle group, indicating that the brain levels of AβPF were significantly lower in the mAb158 3 and 10 mg/kg groups than in the vehicle group.

To 9- to 10-month-old male and female Tg-APP_{ArcSwe} mice (N = 8-10/group), mAb158 (12 mg/kg) or vehicle (PBS) was administered once weekly intraperitoneally for 18 weeks. Brains were harvested 1 to 3 days after the final dose, and the levels of various Aβ species in the brain were measured by ELISA. The areas of Aβ plaques in the cerebral cortex and hippocampus were quantified by immunohistochemistry staining with anti-Aβ40 antibody and by Congo red staining. The brain levels of AβPF were 115 and 484 pmol/L in the mAb158 and vehicle groups, respectively, indicating that the brain levels of AβPF were significantly lower in the mAb158 group than in the vehicle group. There were no differences between the groups in the levels of soluble and insoluble total Aβ, Aβ (1-40), or Aβ (1-42). There were no differences in the Aβ plaque area of the cerebral cortex and hippocampus between the groups.

To 12- to -14-month-old male and female Tg-APP_{ArcSwe} mice (N = 8-9/group), mAb158 (10 mg/kg) or vehicle (PBS) was administered once weekly intraperitoneally for 13 weeks. Brains were harvested 7 days after the final dose, and the levels of various Aβ species in the brain were measured by ELISA. The brain levels of AβPF (mean ± standard error) were 254 ± 25 and 605 ± 49 pmol/L in the mAb158 and vehicle groups, respectively, indicating that the brain levels of AβPF were significantly lower in the mAb158 group than in the vehicle group. The total Aβ (1-40) and total Aβ (1-42) in the brain were significantly lower in the mAb158 group than in the vehicle group.

To 12- to -14-month-old male and female Tg-APP_{ArcSwe} mice (N = 2-7/group), mAb158 (0.3, 1, 3, or 10 mg/kg) or vehicle (PBS) was administered once weekly intraperitoneally for 17 weeks. Brains were harvested and CSF was collected 7 days after the final dose, and the brain levels and CSF levels of various Aβ species were measured by ELISA. The brain levels of AβPF in the mAb158 0.3, 1, 3, and 10 mg/kg groups were lower than those in the vehicle group by 28%, 33%, 54%, and 50%, respectively, and the difference was statistically significant at all dose levels. The CSF AβPF levels did not differ from vehicle at mAb158 0.3, 1, and 3 mg/kg, but were lower than vehicle at mAb158 10 mg/kg by 85%, indicating that the difference was statistically significant. There were no significant differences in the levels of brain total Aβ (x-40), brain total Aβ (x-42), CSF Aβ (1-40), or CSF Aβ (1-42) compared with the vehicle at any dose level of mAb158. There were also no significant differences in the brain levels of soluble Aβ (x-40) and Aβ (1-42) compared with the vehicle at any dose level of mAb158.

To 18- to 24-month-old male and female Tg-APP_{ArcSwe} mice (N = 7-11/group), mAb158 (12 mg/kg) or vehicle (PBS) was administered once weekly intraperitoneally for 14 weeks. Brains were harvested 7 days after the final dose, and the levels of various Aβ species in the brain were measured by ELISA. The brain levels of AβPF in the mAb158 group were lower than those of the vehicle group by 52%, indicating that the difference was statistically significant. The brain levels of soluble Aβ (x-42) were lower in the mAb158 group than in the vehicle group by 56%, indicating that the difference was statistically significant. There were no differences in the brain levels of soluble Aβ (x-40) between the groups.

3.2 Secondary pharmacodynamics

3.2.1 Binding of lecanemab to plasma and CSF proteins (CTD 4.2.1.2.1 [reference data] and 4.2.1.2.2 [reference data])

Proteins bound to lecanemab were immunoprecipitated using brain extracts from cynomolgus monkeys, Hela cells, BE(2)-C cells, SH-SY5Y cells, human CSF, or human plasma, and the protein content was analyzed by liquid chromatography mass spectrometry (LC-MS). A total of 46 proteins were detected in human CSF or human plasma. Three proteins were detected both in human CSF and in human plasma: fibrinogen α chain, β chain, and γ chain.

The binding characteristics of lecanemab and fibrinogen in the presence and absence of AβPF were investigated by immunoprecipitation. Lecanemab was not immunoprecipitated with fibrinogen in the absence of AβPF, while lecanemab was immunoprecipitated with fibrinogen α chain in the presence of AβPF.

Plasma proteins bound to lecanemab were immunoprecipitated using plasma from mice, rats, monkeys, healthy adult humans, and patients with AD, and proteins were identified by Western blotting or mass spectrometry (MS). In all plasma samples, lecanemab was immunoprecipitated with thrombospondin 1 (THBS1), while in plasma from cynomolgus monkeys and patients with AD, lecanemab was immunoprecipitated with 75-80 kDa proteins.[13)] Additionally, the binding affinity of lecanemab or mAb158 for human THBS1 was measured by SPR, and the K_D values were 4 and 6.6 μmol/L for lecanemab and mAb158, respectively.

3.2.2 Prediction of antigenic properties of lecanemab (CTD 4.2.1.2.4 [reference data])

The binding characteristics of nine-amino acid peptides designed to cover the variable region of lecanemab and 34 human leukocyte antigen (HLA) class II allotype were investigated by *in silico* analysis. The results suggested that 7 nine-amino acid peptides had high binding affinity to HLA class II, while 5 nine-amino acid peptides had moderate binding affinity. The sequence homology of the variant region of lecanemab with T cell epitopes identified in the past was analyzed using the basic local alignment search tool (BLAST). The results suggested that F32 on the heavy chain and V83 on the light chain of lecanemab may be T cell epitopes.

3.2.3 T cell response of lecanemab (CTD 4.2.1.2.5 [reference data])

Lecanemab (0 or 300 nmol/L) was added to peripheral blood mononuclear cells (PBMCs) from 25 healthy adults with a wide diversity of HLA. At 5, 6, 7, and 8 days of culture, T cell proliferation was evaluated by ^{3}H-thymidine incorporation assay. A T-cell proliferation-positive result was defined as ≥2-fold increase in ^{3}H-thymidine incorporation from baseline at ≥1 timepoint, with a significant difference compared with culture samples unspiked with lecanemab. According to the definition, 3 of 25 PBMC samples had positive results. The interleukin-2 (IL-2) capture antibody was immobilized onto plates. Peripheral blood mononuclear cells and lecanemab (0 or 300 nmol/L) were added to the plates, and the amount of captured IL-2 on the plate was measured at 8 days of culture. An IL-2 production positive result was defined as ≥2-fold increase in IL-2

13) The 75-80 kDa proteins were not identified.

production from baseline, with a significant difference compared with culture samples unspiked with lecanemab. According to the definition, 2 of 25 PBMC samples had positive results.

3.2.4 Possibility of cerebral microhemorrhage caused by mAb158 (CTD 4.2.1.1.25 [reference data], 4.2.1.1.30 [reference data], 4.2.1.1.31 [reference data], and 4.2.1.1.33 [reference data])

In the studies using Tg-APP_{AreSwe} and Tg2576 mice, histopathological evaluation of the brain was performed. No cerebral microhemorrhage was observed in mice treated with mAb158 (1–50 mg/kg), and no histopathological changes were noted.

3.3 Safety pharmacology

Table 5 shows the results of safety pharmacology studies.

Table 5. Summary of safety pharmacology studies

Item	Test system	Evaluation parameter/technique	Dosage	Route of administration	Finding	CTD
Central nervous system	Cynomolgus monkey (N = 3/sex/group)	General behavior (functional observational battery), tympanic temperature	0,[a] 5, 15, 50 mg/kg	IV	No effects	4.2.3.2.1
Respiratory system	Cynomolgus monkey (N = 3/sex/group)	Respiratory rate, tidal volume, minute ventilation (whole-body plethysmography)	0,[a] 5, 15, 50 mg/kg	IV	No effects	4.2.3.2.1
Cardiovascular system	Cynomolgus monkey (N = 3/sex/group)	Blood pressure, electrocardiogram, heart rate	0,[a] 5, 15, 50 mg/kg	IV	No effects	4.2.3.2.1

a, 25 mmol/L citrate buffer solution containing 125 mmol/L sodium chloride and 0.02% polysorbate 80

3.R Outline of the review conducted by PMDA

3.R.1 Primary pharmacodynamics

The applicant's explanation about lecanemab's mechanism of action by which disease progression is slowed down in patients with early AD:

It has been suggested that among various forms of Aβ species, Aβ oligomers or PF bind to the postsynaptic membrane such as the dendritic spines of neurons, inducing synaptic impairment (*Nat Neurosci.* 2001;4:887-93, *J Neurosci.* 2004;24:10191-200).

The *in vitro* studies showed that lecanemab and mAb158 selectively bound to AβPFs, and the binding affinity of lecanemab and mAb158 for soluble Aβ species increased in proportion to the size of Aβ oligomers, with the binding affinity for AβPF being the highest. Lecanemab and mAb158 inhibited β sheet formation of Aβ oligomers and inhibited AβPF binding to dendritic spines of rat hippocampal neurons (lecanemab, IC_{50} 8.2 nmol/L; mAb158, completely inhibited at 67 nmol/L). In addition, lecanemab and mAb158 inhibited the Aβ oligomer's reduction effect in field excitatory postsynaptic potential in mouse hippocampus slices. The results including the above suggest that lecanemab can inhibit Aβ aggregate formation, thereby inhibiting neuronal disorders induced by Aβ aggregates.

The *in vivo* studies showed that mAb158 decreased the brain levels of AβPF and Aβ plaques in APP^{NL-G-F} mice, Tg2576 mice, and Tg-APP_{ArcSwe} mice. In the study using Tg2576 mice, treatment with mAb158 decreased the number of activated microglia in the brain. Given that activated microglia clustered around Aβ plaques may be involved in the removal of enhanced Aβ aggregation or accumulation (*Am J Pathol.* 1998;152:307-17, *Front Immunol.* 2022;13:856376), it is considered that the decreased number of activated microglia is consistent with the progress of Aβ plaque clearance. The *in vitro* studies showed that lecanemab had binding affinity for human FcγRI and human FcγRIII, which suggested involvement of FcγRI and FcγRIII in lecanemab's Fc-mediated Aβ removal. In another study, the addition of AβPFs to culture of microglia from patients with AD led to uptake of Aβ. The uptake of Aβ into microglia increased in the presence of lecanemab compared with that in the absence of lecanemab, and was reduced by the FcR inhibitor. These results suggest that lecanemab binds to Aβ aggregates, which is likely to promote uptake of Aβ into microglia mediated by FcγRI and FcγRIII.

Taken together, the above results suggest that the opsonization of Aβ aggregates by lecanemab followed by microglial phagocytosis may contribute to the reduction of Aβ levels in the brain by lecanemab. The concentrations of mAb158 in CSF when reduction in the brain levels of AβPF in Tg-APP_{ArcSwe} mice and Tg2576 mice occurred were 27 to 1300 ng/mL and 350 to 1900 ng/mL, respectively. These do not differ significantly from lecanemab concentrations in CSF following administration of 7 lecanemab doses of 10 mg/kg biweekly to patients with mild or moderate AD-D in a clinical pharmacology study (Study 101), 263 and 116 ng/mL at 24 hours and 14 days after the final dose, respectively.

Based on the above, lecanemab is expected to reduce AβPF levels by binding to AβPFs in the human brain, thereby slowing the progression of the disease in patients with early AD.

PMDA's view:
Although there are limitations to use non-clinical data in the evaluation of whether the lecanemab-induced reduction of AβPF levels in the brain is likely to improve clinical symptoms, based on the applicant's explanation, it was concluded that lecanemab can be expected to reduce AβPF levels by binding to AβPFs in the human brain.

3.R.2 Secondary pharmacodynamics

PMDA asked the applicant to explain if there is any possibility that clinically serious concerns will emerge when lecanemab binds to THBS1.

The applicant's explanation:
Thrombospondin 1 is secreted from platelet α granules upon activation following thrombin stimulation, and is believed to be involved in platelet aggregation, inhibition of angiogenesis, tumor infiltration, metastasis, and promotion of immune responses in tumor environments (*J Surg Res.* 2004;122:135-42). Thrombospondin 1 is expressed in many tissues during embryogenesis, while its expression in healthy adults is as low as 50 to 250 ng/mL (*J Surg Res.* 2004;122:135-42). It has been reported that THBS1 expression increases with aging and in age-related conditions including Type 2 diabetes mellitus and cardiovascular disease, and that decreased THBS1 is associated with poor prognosis of malignancy (*Atlas Genet Cytogenet Oncol Haematol.* 2020;24:291-9).

In THBS1-deficient mice, thrombin-induced platelet aggregation was not reduced, and the organs showed no major abnormalities, while increases in the number of white blood cells, monocytes, and eosinophils were observed along with pneumonia (*J Clin Invest.* 1998;101:982-92). Therefore, the reported increase and decrease in THBS1 associated with different diseases mentioned above are considered to be mainly the consequences rather than the causes of diseases. However, given that promotion of immune responses by THBS1 has been suggested (*J Surg Res.* 2004;122:135-42) and pneumonia was observed in THBS1-deficient mice, there is a concern that one of the effects of binding of lecanemab to THBS1 could be exacerbation of pneumonia. Nevertheless, in the toxicity studies of lecanemab, coagulation and other hematology testing and histopathology testing did not reveal findings indicative of THBS1 involvement, such as changes in each blood

cell count, abnormal coagulation parameters, or pneumonia associated with lecanemab. In Study 201 (Core), mild to severe pneumonia occurred in 9 subjects in the lecanemab group (4 subjects in the 5 mg/kg biweekly group, 3 subjects in the 10 mg/kg monthly group, and 2 subjects in the 10 mg/kg biweekly group) and in Study 301 (Core), mild to severe pneumonia occurred in 4 subjects in the lecanemab group. A causal relationship to the study drug was denied for all events.

In view of the above, it is unlikely that clinically serious concerns will emerge when lecanemab binds to THBS1.

PMDA considers that the applicant's explanation is reasonable.

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

The concentrations of lecanemab in serum in rats and monkeys were measured by ELISA. The lower limit of quantitation was 0.25 μg/mL in rats and 0.50 μg/mL in monkeys. The plasma and CSF concentrations of mAb158, the murine IgG2a homologous antibody of lecanemab, were measured by ELISA, with a lower limit of quantitation of 0.2 and 0.002 μg/mL, respectively. Radioactivity levels following administration of ^{125}I-radiolabeled rec158 were measured with a gamma counter.

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

4.1 Absorption

4.1.1 Single-dose studies (CTD 4.2.2.2.1, 4.2.3.1.1, 4.2.3.1.2 [reference data], 4.2.2.2.3 [reference data], and 4.2.2.2.4)

Table 6 shows the PK parameters of mAb158 in plasma or CSF following single dose administration of mAb158 peritoneally to 43-week-old female Tg2576 mice.

Table 6. PK parameters[a] following a single peritoneal dose of mAb158 to aging Tg2576 mice

Dose (mg/kg)	Specimen	C_{max} (μg/mL)	t_{max} (h)	$AUC_{0\text{-}168h}$[b] (μg·h/mL)	$t_{1/2}$ (h)
1	Plasma	11.101	4	1068.135	69.70
	CSF	0.051	72	5.638	—
5	Plasma	52.113	24	6711.346	104.74
	CSF	0.245	24	29.859	—
15	Plasma	170.080	8	17637.855	56.04
	CSF	0.562	24	53.217	—

N = 3–4/timepoint; "—," Not calculated
a, Calculated based on the mean mAb158 concentration in plasma or CSF; b, Final measurement timepoint

Table 7 shows PK parameters of serum lecanemab following administration of a single intravenous dose of lecanemab to male and female rats or a single intravenous or subcutaneous dose of lecanemab to male monkeys. Following intravenous administration of lecanemab 10 mg to male monkeys, the total clearance (CL) of lecanemab was 0.189 ± 0.029 mL/h/kg and the volume of distribution at steady state (V_{ss}) was 65.1 ± 15.5 mL/kg. The absolute bioavailability (BA), which is calculated based on the area under the concentration-

time curve (AUC) from time zero to infinity ($AUC_{0\text{-}inf}$) of lecanemab following subcutaneous administration, was 95.9%.

Table 7. PK parameters of lecanemab following a single intravenous/subcutaneous dose to rats or monkeys

Animal	Route of administration	Dose (mg/kg)	Sex	N	C_{max} (μg/mL)	t_{max} (h)	AUC (μg·h/mL)	$t_{1/2}$ (h)
Rat	IV	10	M	3	279.7 ± 11.6[a]	—	23727.3 ± 711.2[b]	278.1 ± 23.8
			F	3	255.7 ± 17.6[a]	—	23135.8 ± 1561.1[b]	251.3 ± 59.2
		30	M	3	897.9 ± 42.2[a]	—	61222.5 ± 4030.7[b]	229.3 ± 27.8
			F	3	727.6 ± 43.6[a]	—	53621.8 ± 4270.3[b]	207.2 ± 27.3
		100	M	3	2458.9 ± 234.9[a]	—	216832.0 ± 7945.0[b]	226.6 ± 23.5
			F	3	2257.1 ± 275.2[a]	—	188217.9 ± 2825.8[b]	222.9 ± 17.5
Monkey	IV	5	M	3	139.0 ± 35.1[a]	—	21415.4 ± 2193.2[c]	289.3 ± 52.4
		10	M	3	—	—	55100 ± 9100[d]	241.4 ± 49.5
		50	M	3	1336.2 ± 341.7[a]	—	226441.7 ± 16735.6[c]	312.3 ± 22.8
	SC	10	M	3	94.8 ± 6.3	96.0 ± 63.5	52900 ± 4100[d]	270.9 ± 45.1
		50	M	4	472.1 ± 18.2	72.0 ± 27.7	194842.8 ± 22096.0[e]	255.6 ± 51.9

"—," Not calculated

a, $C_{0.083h}$; b, $AUC_{0\text{-}384h}$; c, $AUC_{0\text{-}672h}$; d, $AUC_{0\text{-}inf}$; e, $AUC_{0\text{-}840h}$

4.1.2 Repeated-dose studies (CTD 4.2.3.2.2 and 4.2.3.6.1)

Table 8 shows the PK parameters of serum lecanemab following administration of repeated intravenous doses once weekly for 39 weeks to male and female monkeys.

Table 8. PK parameters of lecanemab in monkeys following repeated intravenous doses once weekly

Dose (mg/kg)	N (Male/female)	Timepoint (Day)	C_{max} (μg/mL)[b]		$AUC_{0\text{-}168h}$ (μg·h/mL)	
			Male	Female	Male	Female
15	4/4	1	421 ± 85	340 ± 32[c]	28100 ± 5700	26900 ± 800[c]
		92	988 ± 157	812 ± 135	106000 ± 36000	92100 ± 16400
		274	1170 ± 300	937 ± 272	120000 ± 41000	103000 ± 29000
50	4/4	1	1520 ± 140	1280 ± 260	114000 ± 6000	96400 ± 18800
		92	3680 ± 440	2950 ± 290	405000 ± 37000	361000 ± 42000
		274	3310 ± 850	2610 ± 390	353000 ± 75000	293000 ± 60000
100[a]	6/6	1	2270 ± 250[d]	2340 ± 270	173000 ± 5000[d]	171000 ± 18000
		92	5390 ± 240	4190 ± 330	584000 ± 57000	485000 ± 37000
		274	4150 ± 280	4760 ± 950	463000 ± 40000	574000 ± 72000

a, Two doses of lecanemab (50 mg/kg each dose) were administered 3 hours apart

b, $C_{0.083h}$ in the 15 mg/kg and 50 mg/kg groups, $C_{3.083h}$ in the 100 mg/kg group

c, N = 3; d, N = 5

Table 9 shows the PK parameters of serum lecanemab following administration of repeated subcutaneous doses once daily for 4 weeks to male and female monkeys.

Table 9. PK parameters of lecanemab in monkeys following repeated subcutaneous doses once daily

Dose (mg/kg)	N (Male/female)	Timepoint (Day)	C_{max} (μg/mL)		$AUC_{0\text{-}24h}$ (μg·h/mL)	
			Male	Female	Male	Female
10	4/4	1	52.4 ± 11.6	54.6 ± 15.1	657 ± 145	797 ± 366
		28	1470 ± 110	1610 ± 170	32000 ± 1300	32600 ± 4000

4.2 Distribution

4.2.1 Tissue distribution (CTD 4.2.2.3.1 [reference data])

To 10-month-old female wild-type mice and 23-month-old female Tg2576 mice, a single dose of 0.37 mg/kg of ^{125}I-radiolabeled rec158, the murine IgG2c homologous antibody of lecanemab, was administered intraperitoneally and tissue distribution of radioactivity at 3, 24, 48, 72, 168, 240, and 336 hours post-dose was evaluated (N = 4/timepoint). In wild-type mice, the radioactivity levels were highest in the liver, and tended to be high in the heart, kidney, lung, and spleen. The radioactivity levels in the brain were low. It has been suggested that in Tg2576 mice, which have higher brain Aβ levels than wild-type mice, radioactivity levels are distributed in a similar manner as in wild-type mice based on the distribution of relative radioactive levels in each tissue, and elimination of radioactivity from the brain did not differ markedly from elimination of radioactivity from blood and other tissue.

4.2.2 Placental transfer

No studies on the placental transfer of lecanemab were conducted. Studies have demonstrated that lecanemab binds to FcRn [see Section "3.1.1.8 Binding affinity for Fc receptor (FcR)"], and IgG binds to FcRn and crosses the placenta in humans (*Nat Rev Immunol.* 2007;7:715-25, *Clin Dev Immunol.* 2012;2012:985646). Based on the above, the applicant stated that lecanemab, an IgG antibody, is likely to cross the placenta to the fetus.

4.2.3 Metabolism and excretion

The applicant's explanation about the metabolism and excretion of lecanemab:

No studies on the metabolism or excretion of lecanemab have been conducted. Lecanemab, an IgG antibody, is considered to be decomposed by intracellular catabolism similarly to other IgG antibodies. Lecanemab is also likely to be excreted in breast milk based on the reports that IgG is excreted in breast milk (*Vaccine.* 2003;21:3374-6, *Pediatr Allergy Immunol.* 2009;20:528-35).

4.R Outline of the review conducted by PMDA

Although no non-clinical pharmacokinetic studies on distribution other than tissue distribution, metabolism, and excretion of lecanemab were conducted, such information can be predicted from already available data. On the basis of the submitted data and the applicant's explanation, PMDA concluded that non-clinical pharmacokinetics of lecanemab has been adequately evaluated.

5. Toxicity and Outline of the Review Conducted by PMDA

The applicant conducted single-dose toxicity studies, repeated-dose toxicity studies, and other toxicity studies (tissue cross reactivity studies and histopathological evaluation in the pharmacology studies). Genetically modified mice, namely, Tg-APP$_{ArcSwe}$ mice and Tg2576 mice, were used in the pharmacology studies in which histopathological evaluation was performed. The murine IgG2a homologous antibody of lecanemab, mAb158, was used as the test substance.

5.1 Single-dose toxicity (CTD 4.2.3.1.1 and 4.2.3.1.2 [reference data])

Single dose toxicity studies were conducted in rats and cynomolgus monkeys (Table 10). There were no deaths or acute toxicity in either study.

Table 10. Single-dose toxicity studies

Test system	Route of administration	Dose (mg/kg)	Major findings	Approximate lethal dose (mg/kg)	CTD
Male/female rat (SD)	IV	0,[a] 10, 30, 100	No noteworthy findings	>100	4.2.3.1.1
Male cynomolgus monkey	IV	5, 50	No noteworthy findings	>50	4.2.3.1.2 (Reference data)

a, 25 mmol/L sodium citrate; 125 mmol/L sodium chloride; 0.02% (w/v) polysorbate 80

5.2 Repeated-dose toxicity (CTD 4.2.3.2.1 and 4.2.3.2.2)

As shown in Table 11, 4-week and 39-week repeated-dose toxicity studies were conducted in cynomolgus monkeys. Findings included high spleen weights and changes in the germinal center in the spleen, indicating immune responses to lecanemab, a heterologous protein, and thus of low toxicological significance. The exposure (AUC for a dosing interval [$AUC_{0-\tau}$]) at the no-observed adverse effect level (NOAEL) for lecanemab was 518500 μg·h/mL (mean for males and females), and twice the $AUC_{0-\tau}$, an estimated AUC from time zero to 2 weeks ($AUC_{0-2week}$), was approximately 27 times the exposure[14] in humans ($AUC_{0-2week}$, 37700 μg·h/mL) at a clinical dose (10 mg/kg).

Table 11. Repeated-dose toxicity studies

Test system	Route of administration	Dosing period	Dose (mg/kg/week)	Major findings	NOAEL (mg/kg/week)	CTD
Male/female cynomolgus monkey	IV	4 weeks (once weekly) + 5-week recovery period	0,[a] 5, 15, 50	At ≥15, high splenic weights, increase/expansion of germinal center in the spleen Reversibility: unknown	50	4.2.3.2.1
Male/female cynomolgus monkey	IV	39 weeks (once weekly) + 13-week recovery period	0,[a] 15, 50, 100	At ≥15, high splenic weights, increase in germinal center in the spleen Reversibility: reversible	100	4.2.3.2.2

a, 25 mmol/L sodium citrate; 125 mmol/L sodium chloride; 0.02% (w/v) polysorbate 80

5.3 Genotoxicity

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

5.4 Carcinogenicity

No standard carcinogenicity studies were conducted because lecanemab may be immunogenic in rodents. The applicant considers that the carcinogenic risks associated with lecanemab are low based on the following factors:

- Lecanemab is an IgG antibody and is therefore not expected to pose genotoxic risks.

[14] The mean exposure at 10 mg/kg in Study 101, a foreign phase I study.

- Lecanemab does not have an effect on immunomodulatory activities (e.g., immunosuppression or immunoproliferative effect) that may lead to carcinogenesis.
- In the repeated-dose toxicity studies using lecanemab, there were no reports of findings that indicate histopathological changes that could be attributed to carcinogenicity or possible immunosuppression.

5.5 Reproductive and developmental toxicity

No reproductive and developmental toxicity studies have been conducted because no animal species develop accumulation of Aβ, the target of lecanemab, during the weeks of reproductive age, as well as for other reasons. The applicant considers that risk of reproductive and developmental toxicity associated with lecanemab is low based on the following factors:

- In mice in which APP expression is reduced or inhibited to reduce Aβ production, fertility was maintained, suggesting that lecanemab, which promotes clearance of Aβ and its aggregates, is not likely to affect fertility and embryo-fetal development.
- In the repeated-dose toxicity studies using lecanemab, no effects on female cycles or male/female reproductive organs were reported.

5.6 Local tolerance

The local tolerance of intravenous lecanemab was evaluated as part of single-dose toxicity studies in rats and monkeys (Table 10) and repeated-dose toxicity studies in monkeys (Table 11). No findings associated with administration of lecanemab were noted at the injection site.

5.7 Other toxicity studies

5.7.1 Tissue cross-reactivity studies (CTD 4.2.3.7.7.2 and 4.2.3.7.7.3)

Frozen sections were prepared from normal tissues of humans, rats, and cynomolgus monkeys, and tissue cross-reactivity of lecanemab was evaluated by immunohistochemistry. No lecanemab-specific staining was noted in any tissue section of rats. In cynomolgus monkey sections, lecanemab-specific staining was observed in the following areas: endocrine cells in the intermediate pituitary gland, cytoplasm of renal proximal tubule epithelial cells, pia mater and subpial perivascular space in the cerebrum, cerebellum, and spinal cord. In human sections, in addition to extracellular Aβ plaques in the cerebrum, lecanemab-specific staining was observed in cytoplasm of various tissues, such as neurons and microglia in the brain nervous tissue; epithelial cells and mononuclear cells in gastrointestinal tissues; pancreatic islet cells.

5.7.2 Histopathological examination in pharmacology studies

Pharmacology studies were conducted in which repeated doses of mAb158 were administered to Tg-APP_{ArcSwe} mice and Tg2576 mice, and histopathological examinations were performed (Table 12). No on-target toxicity of mAb158 was detected, and there were no reports of mAb158-associated cerebral microhemorrhage or inflammatory changes.

Table 12. Histopathological examinations in pharmacological studies

Test system	Route of administration	Dosing period	Dose (mg/kg/week)	Result	CTD
Male/female Tg-APP$_{ArcSwe}$ mouse 18–24 months of age	Intraperitoneal	14 weeks (once weekly)	0,[a] 12	The incidence of cerebral microhemorrhage in the mAb158 group was comparable to that of the control group.	4.2.1.1.25 (reference data)
Male/female Tg-APP$_{ArcSwe}$ mouse and wild-type mouse 12–14 months of age	Intraperitoneal	17 weeks (once weekly)	0,[a] 0.3, 1, 3, 10	No noteworthy findings	4.2.1.1.26 (reference data)
Female Tg2576 mouse 12.5 months of age	Intraperitoneal	18 weeks (once weekly)	0,[a] 12, 24	The incidence of cerebral microhemorrhage in the mAb158 12 mg/kg group was comparable to that of the control group	4.2.1.1.31 (reference data)
Female Tg2576 mouse 4 months of age	Intraperitoneal	18 weeks (once weekly)	0,[a] 3, 6, 12	No noteworthy findings	4.2.1.1.30 (reference data)
Female Tg2576 mouse 12 months of age	Intraperitoneal	18 weeks (once weekly)	0,[a] 1, 5, 15, 50	No noteworthy findings	4.2.1.1.33 (reference data)

a, PBS

5.R Outline of the review conducted by PMDA

5.R.1 Cerebrovascular findings

Although no cerebral microhemorrhages or inflammatory changes were noted in the repeated-dose toxicity studies using lecanemab and pharmacological studies using mAb158, there have been reports of cerebral microhemorrhages in non-clinical and clinical studies of other anti-Aβ antibodies, which remove Aβ, similarly to lecanemab. PMDA asked the applicant to explain the factors that had led to the difference in the incidence of cerebrovascular findings between lecanemab and other anti-Aβ antibodies, and whether there is any possibility that cerebral microhemorrhage would occur after administration of lecanemab in clinical use.

The applicant's explanation:

Besides lecanemab, anti-Aβ antibodies that remove Aβ include aducanumab and its mouse homologue, ^{ch}12F6A, and the mouse homologue of bapineuzumab, 3D6. An increase in cerebral microhemorrhage has been reported in Tg mouse model studies associated with these and many other anti-Aβ antibodies (Table 13). It has been surmised that the increase in cerebral microhemorrhage is attributable to activation of phagocytosis resulting from Aβ plaque clearance and binding of IgG to FcR in the brain (e.g., *Front Neurosci.* 2014;8:235). While a decrease in Aβ plaques in the brain was observed in the pharmacology studies of mAb158, there was no increase in cerebral microhemorrhage [see Section "5.7.2 Histopathological examination in pharmacology studies"]. Other anti-Aβ antibodies mentioned above target Aβ species differently from the Aβ species targeted by lecanemab. Lecanemab and mAb158 are designed to selectively bind to AβPFs. The binding affinity of lecanemab and mAb158 for AβPFs is ≥1000 times that of their affinity for Aβ monomers, and is also higher than the affinity for Aβ fibrils and for Aβ oligomers [see Sections "3.1.1.1 Binding characteristics and selectivity of lecanemab for Aβ" and "3.1.1.2 Binding characteristics and selectivity of lecanemab and mAb158 for Aβ"]. Therefore, it is considered that the difference in the incidence of cerebral microhemorrhage is due to the difference in the affinity for target molecules.

Table 13. Cerebral microhemorrhages reported in non-clinical studies on lecanemab, mAb158, and other anti-Aβ antibodies

Antibody	Target molecule (Structure to bind and recognition site)	Effects on Aβ plaques in the brain of Tg mouse model	Cerebral microhemorrhage in Tg mouse model
Lecanemab and mAb158	Aβ oligomers, AβPFs Aβ peptide residues 2-3	Plaque reduction	None
Aducanumab and ^{ch}12F6A[a]	Aβ oligomers, AβPFs, Aβ fibrils, Aβ plaques Aβ peptide residues 3-7	Not known	Microhemorrhage increase
3D6[b]	Aβ monomers, Aβ oligomers, Aβ fibrils, Aβ peptide residues 1-5	Plaque reduction	Microhemorrhage increase
6E10[c]	Aβ monomers, Aβ oligomers, Aβ plaques, Aβ peptide residues 1-16 or 17	Plaque reduction	Microhemorrhage increase
2286[d]	Not known Aβ peptide residues 28-40	Plaque reduction	Microhemorrhage increase
2H6[e]	Not known Aβ peptide residues 33-40	Plaque reduction	Microhemorrhage increase
10D5[f]	Not known Aβ peptide residues 3-7	Plaque reduction	Microhemorrhage increase

a, FDA non-clinical review BLA 761178
b, *J Neurosci.* 2005;25:629-36, *Alzheimers Dement.* 2013;9:S105-15
c, *J Negat Results Biomed.* 2017;16:1, *Proc Natl Acad Sci USA.* 2009;106:4501-6
d, *J Neuroinflammation.*2004;1:24, *CNS Neurol Disord Drug Targets.* 2009;8:50-64
e, *J Neurosci.* 2006;26:5340-6, *CNS Neurol Disord Drug Targets.* 2009;8:50-64
f, *Mol Neurodegener.* 2017;12:12

The incidence of cerebral microhemorrhages in the clinical studies of lecanemab and other anti-Aβ antibodies, namely, aducanumab and donanemab, was evaluated (Table 14). In humans, the incidence of cerebral microhemorrhages after treatment with lecanemab was not higher than that with other anti-Aβ antibodies.

Table 14. Incidence of cerebral microhemorrhages in clinical studies of lecanemab, aducanumab, and donanemab

Antibody	Number of patients and frequency of cerebral microhemorrhage			
Lecanemab[a]	Placebo	10 mg/kg		
	68/897 7.6%	126/898 14.0%		
Aducanumab[b]	Placebo	3 mg/kg	6 mg/kg	10 mg/kg
	71/1087 6.5%	141/760 18.6%	35/333 10.5%	212/1105 19.2%
Donanemab[c]	Placebo	700 mg/1400 mg		
	6/125 4.8%	26/131 19.8%		

a, Study 301 Core, treatment for 78 weeks
b, Pooled data from ENGAGE study/EMERGE study (FDA Medical Review BLA 761178), treatment for 78 weeks
c, TRIAL BLAZER-ALZ study (*N Engl J Med.* 2021;384:1691-704), treatment for 72 weeks

PMDA's view:

Although no increase in cerebral microhemorrhage was reported in the non-clinical studies of mAb158, given the mechanism of action of cerebral microhemorrhage as described by the applicant, the possibility that cerebral microhemorrhage associated with amyloid-related imaging abnormalities (ARIA) could be caused when lecanemab is administered cannot be ruled out. Whether the risk for microhemorrhage associated with ARIA is acceptable and whether cautionary statements regarding the risk are appropriate will be discussed in Section "7.R.4.1 Amyloid-related imaging abnormalities" based on the clinical study results.

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

Unless otherwise stated, PK parameters are expressed in mean ± standard deviation.

6.1 Summary of biopharmaceutic studies and associated analytical methods

In Study 101, a foreign phase I study in patients with mild to moderate AD-D, and Study 104, a Japanese phase I study in patients with early AD, a formulation manufactured by the manufacturing process of [redacted] was used. In Study 201, a global phase II study in patients with early AD, a formulation manufactured by the manufacturing process of [redacted] was used, while in Study 301, a global phase III study in patients with early AD, a formulation manufactured by the manufacturing process of [redacted] was used. Comparability in terms of quality between formulations manufactured by different manufacturing processes of Process A-1, Process B-1, Process C-1, and Process C-2 has been demonstrated.

The serum concentrations of lecanemab were measured by ELISA or immunopurification (IP)-liquid chromatography coupled with tandem mass spectrometry (LC-MS/MS), with the lower limit of quantitation being 6.00 and 0.500 μg/mL, respectively. Lecanemab concentrations in CSF were measured by electrochemiluminescence (ECL) or IP-LC-MS/MS, with the lower limit of quantitation being 3.00 and 5.00 ng/mL, respectively.

Lecanemab anti-drug antibodies (ADA) and neutralizing antibodies in serum were measured by ECL. The lower limit of quantitation for ADA was 1.09 to 9.77 ng/mL, and the detection sensitivity for neutralizing antibodies was 584 or 1385 ng/mL.

6.2 Clinical pharmacology

6.2.1 Investigations in patients

6.2.1.1 Single-dose and multiple-dose intravenous administration studies in patients with mild to moderate AD-D (Study 101; CTD 5.3.4.2.1 and 5.3.4.2.2 [August 2010 to September 2012])

Table 15 shows the PK parameters of lecanemab in serum after a single intravenous dose of lecanemab 0.3 to 15 mg/kg administered to non-Japanese patients with mild to moderate AD-D. The CSF lecanemab concentration at 24 hours after a single intravenous dose of lecanemab 15 mg/kg was 96.3 ± 45.1 ng/mL, which is 0.043% of the serum concentration.

After administration of lecanemab, 1 subject (0.3 mg/kg), 1 subject (3.0 mg/kg), 5 subjects (10 mg/kg), and 4 subjects (15 mg/kg) tested positive for ADA.[15)]

[15)] Subjects in whom ADA had not been detected at baseline and after administration with lecanemab ADA were detected.

Table 15. PK parameters of lecanemab in serum after a single intravenous dose

Dose (mg/kg)	N	C_{max} (μg/mL)	t_{max}[a] (h)	$AUC_{0\text{-}inf}$ (μg·h/mL)	$t_{1/2}$ (h)
0.3	6	8.50 ± 2.42	2.20	—	—
1	6	24.7 ± 3.62	1.78	—	103[b]
3	6	74.2 ± 11.1	1.83	7430 ± 1210	83.5 ± 13.7
10	6	264 ± 32.4	2.00	38000 ± 7340	165 ± 45.5
15	6	418 ± 54.5	2.00	66900 ± 17600	174 ± 36.1

a, Median; b, N = 1; "—," Not calculated

Table 16 shows the PK parameters of lecanemab in serum after lecanemab 0.3, 1, or 3 mg/kg every 4 weeks (total of 4 doses) or lecanemab 10 mg/kg biweekly (total of 7 doses) was administered intravenously to non-Japanese patients with mild to moderate AD-D. When lecanemab 10 mg/kg was administered biweekly for a total of 7 doses, CSF lecanemab concentrations at 24 hours and 14 days after the seventh dose were 263 ± 106 and 116 ± 109 ng/mL, respectively, corresponding to 0.133% and 0.290% of the respective serum concentrations.

After administration of the multiple doses, 1 subject (1 mg/kg), 2 subjects (3 mg/kg), and 4 subjects (10 mg/kg) tested positive for ADA.[15)]

Table 16. PK parameters of lecanemab in serum after multiple intravenous doses

Dose (mg/kg)	N	Dosing day (Day)	C_{max} (μg/mL)	t_{max}[a] (h)	$AUC_{0\text{-}24h}$ (μg·h/mL)	$AUC_{0\text{-}\tau}$ (μg·h/mL)	$t_{1/2}$ (h)
0.3[e]	6	1	7.62 ± 0.63[b]	1.75[b]	156 ± 12.1[c]	—	—
	6	84	7.26 ± 1.53	2.32	133 ± 23.4	—	—
1[e]	6	1	30.9 ± 3.54	2.00	548 ± 68.9	—	133 ± 20.6[d]
	6	84	30.6 ± 4.59[d]	1.61[d]	470 ± 110[c]	—	—
3[e]	6	1	81.4 ± 16.2	2.08	1380 ± 339	—	133 ± 27.4
	6	84	68.8 ± 8.98[b]	2.10[b]	1220 ± 132[b]	—	—
10[f]	6	1	267 ± 61.8	1.67	4750 ± 1210	27200 ± 8820	105 ± 22.1
	6	84	307 ± 70.2	1.88	5720 ± 1230	37700 ± 9110	127 ± 29.9

a, Median; b, N = 5; c, N = 3; d, N = 4; e, Administered every 4 weeks; f, Administered biweekly; "—," Not calculated

6.2.1.2 Single-dose and multiple-dose studies in patients with early AD (Study 104, CTD 5.3.4.2.3, 5.3.4.2.4, and 5.3.4.2.5 [September 2013 to March 2015])

A single dose of lecanemab 2.5, 5, or 10 mg/kg was intravenously administered to Japanese patients with early AD, and after a 6-week washout period, lecanemab was intravenously administered biweekly (total of 5 doses). Table 17 shows PK parameters of lecanemab in serum. When lecanemab 2.5, 5, or 10 mg/kg was administered biweekly for a total of 4 doses, CSF lecanemab concentrations at 14 days after the final dose were 70.7, 120, and 274 ng/mL, respectively, which correspond to 0.729%, 0.645%, and 0.803% of the respective serum concentration, indicating similar concentrations independent of lecanemab dose levels.

After administration of lecanemab, 5 subjects (2.5 mg/kg), 4 subjects (5 mg/kg), and 6 subjects (10 mg/kg) tested positive for ADA.[15)] Among these subjects, 7 subjects tested positive for neutralizing antibodies.

Table 17. PK parameters of lecanemab in serum after a single intravenous dose and multiple intravenous doses

Dose (mg/kg)	N	C_{max} (μg/mL)	t_{max}[a] (h)	$AUC_{0\text{-}inf}$ (μg·h/mL)	$AUC_{0\text{-}\tau}$ (μg·h/mL)	$t_{1/2}$ (h)	CL (mL/h/kg)	V_{ss} (mL/kg)
Single dose administration								
2.5	6	64.2 ± 13.6	2.140	7320 ± 1120	—	153 ± 30.0	0.349 ± 0.0531	62.0 ± 15.5
5	6	133 ± 9.14	2.055	18200 ± 6970	—	149 ± 52.0	0.310 ± 0.117	53.1 ± 13.7
10	7	235 ± 34.1	2.080	33000 ± 9800	—	159 ± 16.0	0.325 ± 0.0934	61.9 ± 12.2
Multiple dose administration								
2.5	6	72.8 ± 19.4	1.150	—	8980 ± 1690	—	—	—
5	5	154 ± 26.3	1.920	—	22700 ± 7790	—	—	—
10	6	299 ± 45.7	2.010	—	39500 ± 7330	—	—	—

a, Median; "—," Not calculated

6.2.1.3 Population pharmacokinetic (PPK) analysis (CTD 5.3.3.5.1)

A population pharmacokinetic (PPK) analysis was performed on serum lecanemab concentration data (1,619 subjects; 21,929 timepoints) from the foreign phase I study (Study 101), Japanese phase I study (Study 104), global phase II study (Study 201), and global phase III study (Study 301).

The PK of lecanemab was described by a two-compartment model with linear elimination from the central compartment. The subject characteristic factors for the PPK analysis were as follows: sex (819 males and 800 females); race (1,307 Caucasian, 48 Black, 21 Asian [excluding Japanese, Chinese, and South Korean], 138 Japanese, 6 Chinese, 54 South Korean, 45 other race); presence/absence of ADA at blood sampling (ADA present in 1,225 samples and absent in 20,703 samples); age, 72 years [50, 93] (median value [Min, Max], the same applies hereinafter); body weight, 72 kg [37.7, 130.5]; albumin, 43 g/L [35, 54]; and ADA titer 16 [1, 50000]. All of these factors were the candidate covariates on PK parameters. In the final model, the following were selected as statistically significant covariates: presence/absence of ADA, body weight, albumin, and sex (for CL); sex, body weight, and race (for central volume of distribution [V_c]); and race (for peripheral volume of distribution [V_p]). The extent of the effect on PK parameters of lecanemab was not clinically significant for any of the covariates.

The population mean (relative standard error) of the parameters for the final model was 0.0154 L/h (1.60%) for CL, 3.24 L (0.799%) for V_c, 2.00 L (4.09%) for V_p, and 0.00718 L/h (4.23%) for clearance between compartments.

6.2.2 Investigations on intrinsic factors

6.2.2.1 Effects of hepatic impairment and renal impairment on lecanemab PK

The applicant's explanation:

Although no clinical pharmacology studies of lecanemab in patients with hepatic impairment or renal impairment were conducted, given that lecanemab is a humanized IgG1 monoclonal antibody, and like other endogenous IgG antibodies, lecanemab is not metabolized by liver drug-metabolizing enzyme, and is broken down into peptides and amino acids by catabolism. Lecanemab is also a high molecular compound (molecular

weight, approximately 150,000), and thus it is unlikely to be excreted from the kidneys as an unchanged compound.

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 PK of lecanemab between Japanese and non-Japanese populations:

On the basis of the results from the foreign phase I study (Study 101) and the Japanese phase I study (Study 104), the differences in PK between Japanese and non-Japanese populations after a single dose of lecanemab 10 mg/kg (Tables 15 and 17) and after multiple doses of lecanemab 10 mg/kg biweekly (Tables 16 and 17) were investigated. The maximum observed concentration (C_{max}) and AUC from time zero to infinity ($AUC_{0\text{-}inf}$) after a single dose of lecanemab 10 mg/kg and C_{max} and $AUC_{0\text{-}\tau}$ at steady state after biweekly dose of lecanemab 10 mg/kg were similar between Japanese and non-Japanese subjects.

In the PPK analysis using data from Studies 101, 104, 201, and 301, race and body weight were selected as significant covariates for CL, V_c, and V_p. Neither race nor body weight had a significant effect on C_{max} or AUC after lecanemab 10 mg/kg was administered biweekly.

On the basis of the above, it is considered that there are no clear differences in the PK of lecanemab between Japanese and non-Japanese populations.

PMDA concluded that the applicant's explanation that there are no clear differences in the PK of lecanemab 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 subjects who tested positive for ADA[15)] and those who tested positive for neutralizing antibodies in the lecanemab group in Studies 201 and 301.

Table 18. Proportion of subjects who tested positive for ADA[15)] and those who tested positive for neutralizing antibodies in the lecanemab group in Studies 201 and 301[a]

Study	Lecanemab	
	ADA-positive	Neutralizing antibody-positive[b]
Study 201 Core (10 mg/kg, once a month)	61.0 (150/246)	19.3 (29/150)
Study 201 Core (10 mg/kg, biweekly)	40.9 (63/154)	25.4 (16/63)
Study 201 OLE	7.1 (16/224)	0 (0/11)
Study 301 Core	5.5 (49/884)	4.1 (2/49)
Study 301 OLE	5.7 (50/884)	4.0 (2/50)

% (n/N)

a, The validation test method used for measurement in Study 201 Core is different from that used in Study 201 OLE, Study 301 Core, and Study 301 OLE; b, the denominator is subjects who tested positive for ADA

The results of PPK analysis show that the C_{max} and AUC in subjects who tested positive for ADA[15)] were comparable to those in subjects who tested negative for ADA, suggesting that the PK is not markedly affected by the presence of ADA.

Given that there was no clear relationship between the onset of infusion reaction and the occurrence of ADA [see Section "7.R.4.3 Infusion reaction"], the occurrence of ADA is not considered to affect the safety or other aspects of lecanemab.

PMDA considers that the applicant's explanation that no results from clinical studies suggest that ADA or neutralizing antibodies have a significant effect on the PK, safety, and other aspects of lecanemab is reasonable.

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 3 studies summarized in Table 19 [see Section "6. Summary of Biopharmaceutic Studies and Associated Analytical Methods, Clinical Pharmacology, and Outline of the Review Conducted by PMDA" for PK].

Table 19. Outline of main clinical studies

Data	Location	Study identifier	Phase	Study population	Number of subjects enrolled	Summary of dosage regimen	Main endpoints
Evaluation	Japan	104	I	Patients with early AD	26	A single intravenous dose of placebo, lecanemab 2.5, 5, or 10 mg/kg was administered, and after a 6-week washout period, intravenous doses were administered biweekly for a total of 5 doses	Safety PK
	Global	201 Core study	II		856	Intravenous doses of placebo, lecanemab 2.5, 5, or 10 mg/kg were administered biweekly, or lecanemab 5 or 10 mg/kg was administered once a month for 18 months	Efficacy Safety Dose-response
		201 OLE			180	Intravenous doses of lecanemab 10 mg/kg were administered biweekly for 60 months	Efficacy Safety
		301 Core study	III		1795	Intravenous doses of placebo or lecanemab 10 mg/kg were administered biweekly for 18 months	Efficacy Safety
		301 OLE			964[a]	Intravenous doses of lecanemab 10 mg/kg were administered biweekly for 48 months	

a, Number of subjects treated during OLE

7.1 Japanese phase I study (Study 104, CTD 5.3.4.2.3, 5.3.4.2.4, and 5.3.4.2.5 [September 2013 to March 2015])

A randomized, double-blind study was conducted at 7 study centers in Japan to investigate the safety and PK of lecanemab in Japanese patients with early AD (target sample size, 24 subjects).

Following a 60-day run-in period, the treatment period lasted for 14 weeks. On Day 1, a single dose of placebo, lecanemab 2.5 mg/kg (Cohort 1), 5 mg/kg (Cohort 2), or 10 mg/kg (Cohort 3) was to be administered intravenously, and after a 6-week washout period, a total of 5 doses were to be administered intravenously biweekly.

Study drug treatment was to be discontinued if any of the following occurred:

- Brain magnetic resonance imaging (MRI) results indicate the following
  - Vasogenic cerebral edema based on MRI findings
  - Cerebral hemorrhage, superficial siderosis, symptomatic cerebral microhemorrhage based on MRI findings
- When the following symptoms are observed
  - Grade ≥3 hypersensitivity according to National Cancer Institute-common terminology criteria for adverse events (NCI-CTCAE) version 3.0
  - Symptoms consistent with meningoencephalitis
  - Continuous increase in C-reactive protein (CRP) and fibrinogen (continuous increase from baseline by ≥25%)
  - Other dose limiting toxicities, or any other symptoms, which, in the opinion of the principal investigator and sponsor, jeopardize subject safety and make it unacceptable to continue treatment

Key inclusion criteria were patients with early AD aged ≥50 years and ≤90 years who met the following criteria.

Patients with MCI due to AD

- Cohort 1, meeting the core clinical criteria for MCI due to AD as defined by the National Institute of Aging-Alzheimer's Association Workgroup (NIA-AA); Cohorts 2 and 3, meeting the diagnostic criteria for MCI due to AD at intermediate likelihood as defined by the NIA-AA
- Clinical Dementia Rating (CDR) score of 0.5 and CDR Memory Box score of ≥0.5 at screening
- Complaints of a history of subjective memory decline with onset and slow progression ≥1 year before screening; or report of a history of subjective memory decline with slow progression ≥1 year before screening by informant or physician
- 1 to 1.5 standard deviations below[16] age-adjusted mean in the Wechsler Memory Scale-Revised (WMS-R) Logical Memory II (delayed recall) score at screening

Patients with mild AD-D

- Meeting the NIA-AA core clinical criteria for probable AD dementia
- CDR score of 0.5 or 1 and CDR Memory Box score of ≥0.5 at screening

All subjects

- Mini-Mental State Examination (MMSE) score of ≥22 and ≤30 at screening
- Cohorts 2 and 3: positive amyloid load as indicated by positron emission tomography (PET) at screening
- No clinically significant lesions on MRI at screening such as:
  - Four or more cerebral microhemorrhages (≤10 mm at the greatest diameter), symptomatic cerebral microhemorrhage, cerebral hemorrhages >10 mm at greatest diameter, superficial siderosis, vasogenic cerebral edema, brain contusion, encephalomalacia, aneurysm, vascular malformation, space occupying lesions (e.g., arachnoid cyst), brain tumors (e.g., meningioma).
- In Cohort 3, the *APOE* genotype is not homozygous *APOE4* (*ε4/ε4*)

[16] ≤15 for age 50 to 64 years, ≤12 for age 65 to 69 years, ≤11 for age 70 to 74 years, ≤9 for age 75 to 79 years, and ≤7 for age 80 to 90 years

Among symptomatic AD medications, the ongoing treatment dose of cholinesterase (ChE) inhibitors must be stable ≥12 weeks prior to the start of the treatment period. Patients who had been on memantine hydrochloride (memantine) were not allowed to be enrolled in the study.

Of the randomized 26 subjects, 24 subjects (5 subjects in placebo and 19 subjects in the lecanemab) received the study drug, and were included in the safety analysis set.

Table 20 shows the incidence of adverse events.

Table 20. Incidence of adverse events (Safety analysis set)

	Placebo (N = 5)	Lecanemab		
		Cohort 1 (2.5 mg/kg, biweekly) (N = 6)	Cohort 2 (5 mg/kg, biweekly) (N = 6)	Cohort 3 (10 mg/kg, biweekly) (N = 7)
All adverse events	80.0 (4)	83.3 (5)	83.3 (5)	71.4 (5)
Main events[a]				
Atrial fibrillation	0 (0)	0 (0)	0 (0)	28.6 (2)
Cerebral microhaemorrhage	0 (0)	0 (0)	0 (0)	28.6 (2)
Headache	20.0 (1)	33.3 (2)	0 (0)	14.3 (1)
Nasopharyngitis	40.0 (2)	0 (0)	0 (0)	14.3 (1)
Orthostatic hypotension	60.0 (3)	50.0 (3)	33.3 (2)	0 (0)

% (n)
a, Adverse events occurring in ≥2 subjects in any group, i.e., placebo group or any cohort of the lecanemab group

No adverse events led to death or treatment discontinuation. Serious adverse events occurred in 1 subject (headache) in Cohort 1 (lecanemab 2.5 mg/kg biweekly) and 1 subject (pancreatitis acute) in Cohort 2 (lecanemab 5 mg/kg biweekly), and a causal relationship to the study drug was denied for both cases.

7.2 Global phase II study (Study 201, CTD 5.3.5.1.1, 5.3.5.1.2, 5.3.5.1.3, and 5.3.5.1.8 [ongoing since December 2012, data cut-off in April 2022])

A randomized, double-blind, parallel-group study was conducted at 149 study centers in Japan and other countries to investigate the safety, tolerability, and efficacy of lecanemab in patients with early AD (MCI due to AD–intermediate likelihood[17)] and mild AD-D[18)]) (target sample size, 800 subjects[19)]).

The duration of the Core study was 21 months at maximum after randomization (up to an 18-month treatment period plus a 3-month follow-up). After the completion of the analyses for the Core study (July 2018), the Core study was followed by an open-label extension (OLE) phase for up to 63 months (up to a 60-month treatment

17) Subjects who meet the NIA-AA core clinical criteria for MCI due to AD with its likelihood being classified as intermediate, have a CDR score of 0.5 and a Memory Box score of ≥0.5 at Screening and Baseline, and report a history of subjective memory decline with gradual onset and slow progression over the last 1 year before Screening.

18) Subjects who meet the NIA-AA core clinical criteria for probable AD-D and have a CDR score of 0.5 to 1.0 and a Memory Box score of ≥0.5 at Screening and Baseline.

19) Simulations showed that with a sample size of 800, the superiority of lecanemab ED_{90} to placebo by a clinically meaningful difference (defined as the difference to slow progression of decline in ADCOMS by at least 25% compared with placebo after 1 year of lecanemab treatment) can be detected at a probability of >95% (for each interim analysis) and >80% (for the final analysis) in terms of change from baseline in ADCOMS at Month 12, the primary endpoint. In the study, patients were to be recruited so that the MCI due to AD group and the mild AD-D group represent ≥60% and ≥30%, respectively, of the overall patients.

period plus a 3-month follow-up), which was initiated after the gap period (ranging from 9 to 59 months, with a mean of 24 months). In the following sections, in addition to the results for the overall population, the results for the Japanese population are also provided for the Core study, a phase important for the evaluation of efficacy and safety in Japanese patients.

(a) Core study

The first 196 subjects were randomly assigned[20] to the placebo, lecanemab 2.5 mg/kg biweekly (once every 2 weeks), 5 mg/kg monthly, 5 mg/kg biweekly, 10 mg/kg monthly, or 10 mg/kg biweekly groups at a ratio of 2:1:1:1:1:1, and after the 196th subject, the allocation probability for each group was changed according to the results for each prespecified interim analysis using Bayesian response-adaptive randomization (RAR).[21] The interim analyses and RAR were conducted by an external independent entity responsible for analyses, and the results of interim analyses and operation of RAR were monitored by the independent interim monitoring committee. In Study 201, the results of the interim analysis did not meet the criteria for early termination due to futility nor did they meet the criteria for early termination for efficacy, and the Core study continued until sufficient data for the final analysis were accrued. Amyloid-related imaging abnormalities-edema/effusion (ARIA-E) occurred at the beginning of Study 201 Core. After the incidence of ARIA-E, the protocols were amended as follows: from the fourth revision (July 2014), the protocol was amended to no longer randomize homozygous apolipoprotein E ε4 (ApoE ε4) allele carriers to the 10 mg/kg biweekly group, and from the fifth revision (August 2014), the protocol was amended to no longer randomize heterozygous ApoE ε4 carriers to the 10 mg/kg biweekly group.[22] The RAR algorithm was modified before conducting an interim analysis at the time of enrollment of the 350th subject to consider ApoE ε4 carrier status.[23]

In the treatment period, placebo, lecanemab 2.5, 5, or 10 mg/kg was to be administered intravenously biweekly or monthly (lecanemab 2.5 mg/kg was administered biweekly only) (as mentioned above, 10 mg/kg biweekly treatment for ApoE ε4 carriers was discontinued during the study).

Study drug treatment was to be discontinued if ARIA-E or amyloid-related imaging abnormalities-hemorrhage or superficial siderosis (ARIA-H), namely, cerebral hemorrhage, superficial siderosis, or symptomatic cerebral microhemorrhage occurred.

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[20] Randomization was stratified by disease stage (MCI due to AD or mild AD-D), ApoE ε4 carrier status (carrier or non-carrier), and use of symptomatic AD medications (concurrent use of ChE inhibitor and/or memantine, yes/no).

[21] After196 subjects were accrued, interim analyses (including decision on early termination due to futility or early termination for efficacy) on ADCOMS data were carried out for every additional 50 subjects up to 800 subjects. When more than 800 subjects were accrued, similar interim analyses were performed every 3 months for a total of 3 times. On the basis of the results of each interim analysis, the allocation probability for each group was updated (the allocation probability for each group was updated by weighting variance components, and the allocation probability for placebo was to correspond to that for lecanemab dose regimen most likely to be the ED_{90}).

[22] During Study 201 Core, the Data and Safety Monitoring Board evaluated serious adverse reaction data, and recommended that homozygous ApoE ε4 carriers no longer be allocated to the lecanemab10 mg/kg biweekly regimen. Following the recommendation, EMA issued a request to discontinue allocation of ApoE ε4 carriers (heterozygous and homozygous) to the 10 mg/kg biweekly regimen, and to promptly discontinue studies of ApoE ε4 carriers (heterozygous and homozygous) in the 10 mg/kg biweekly group who had been on treatment for less than 6 months.

[23] The RAR algorithm was modified to implement interim analyses and update allocation probabilities by ApoE ε4 carrier status (carrier and non-carrier).

Key inclusion criteria were patients with early AD aged 50 to 90 years who met the following criteria.

- 1 standard deviation below age-adjusted mean in the WMS-IV LM II score (≤15 for age 50 to 64 years, ≤12 for age 65 to 69 years, ≤11 for age 70 to 74 years, ≤9 for age 75 to 79 years, ≤7 for age 80 to 90 years)
- Objective impairment in episodic memory is demonstrated
- Positive amyloid load as indicated by amyloid PET assessment of PET imaging agent uptake into the brain or CSF assessment of Aβ (1-42)
- MMSE score of ≥22 and ≤30[24] at Screening and Baseline
- Geriatric depression scale (GDS) score of <8 at Screening
- The brain MRI scan at Screening indicates no clinically significant findings such as the following:
  - Five or more cerebral microhemorrhages (≤10 mm at the greatest diameter)
  - A cerebral hemorrhage (>10 mm at the greatest diameter)
  - Superficial siderosis
  - Vasogenic brain edema
  - Cerebral contusion, encephalomalacia, aneurysm, vascular malformation, or infective lesions
  - Multiple lacunar infarction, stroke involving a major vascular territory, severe small vessel, or white matter disease
  - Space occupying lesions or brain tumors (however, lesions diagnosed as meningiomas or arachnoid cysts <1 cm at the greatest diameter are not exclusionary)

The ongoing treatment dose level of symptomatic AD medications (ChE inhibitors and/or memantine) must be stable ≥12 weeks prior to baseline throughout the Core study period. In Japan, patients who have been on memantine were not allowed to be enrolled in the study.

The necessity of prophylactic medications before administration of the next dose of the study drug to minimize immune responses or infusion reaction should be decided after evaluating the subject's immune responses to the study drug by the principal investigator based on the clinical findings and laboratory test results.

Overall population

Of the 856 randomized subjects (247 subjects [placebo], 52 subjects [lecanemab 2.5 mg/kg biweekly], 51 subjects [lecanemab 5 mg/kg monthly], 92 subjects [lecanemab 5 mg/kg biweekly], 253 subjects [lecanemab 10 mg/kg monthly], and 161 subjects [lecanemab 10 mg/kg biweekly]; the same applies hereinafter for the order of assigned groups), 854 subjects (245 subjects, 52 subjects, 51 subjects, 92 subjects, 253 subjects, and 161 subjects) received the study drug and were included in the safety analysis set. Of the safety analysis set, 825 subjects (238 subjects, 52 subjects, 48 subjects, 89 subjects, 246 subjects, and 152 subjects) had evaluable data for the primary efficacy endpoint at baseline and ≥1 timepoint post-study dose, and were included in the full analysis set (FAS), which was the primary efficacy analysis set. A total of 315 subjects[25] (99 subjects, 28 subjects, 28 subjects, 27 subjects, 89 subjects, and 44 subjects) who had data that could be used to calculate ≥1 pharmacodynamic (PD) parameter were included in the PD analysis set. A total of 302 subjects (68 subjects,

[24] ≤28 was used in the UK, Spain, Germany, Sweden, France, and the Netherlands.
[25] The number of subjects with amyloid PET scan data.

17 subjects, 14 subjects, 31 subjects, 98 subjects, and 74 subjects) discontinued from the study, with common reasons for discontinuation being "withdrawal of consent" (99 subjects total; 23 subjects, 1 subject, 5 subjects, 13 subjects, 37 subjects, and 20 subjects), "adverse events" (56 subjects total; 10 subjects, 4 subjects, 2 subjects, 5 subjects, 23 subjects, and 12 subjects), and "other reasons" (79 subjects total; 13 subjects, 7 subjects, 4 subjects, 4 subjects, 20 subjects, and 31 subjects). The category of "other reasons" includes 25 subjects in the lecanemab 10 mg/kg biweekly group who were ApoE ε4 carriers and had been assigned to the treatment and then discontinued the study at the request of European Medicines Agency (EMA)[22]; this applied to subjects who had been on the treatment for less than 6 months. Subjects who received concomitant[26] AD medications were as follows: donepezil hydrochloride (donepezil) (367 subjects total; 97 subjects, 24 subjects, 19 subjects, 46 subjects, 109 subjects, and 72 subjects), galantamine hydrobromide (galantamine) (29 subjects total; 8 subjects, 2 subjects, 3 subjects, 1 subject, 11 subjects, and 4 subjects), rivastigmine (86 subjects total; 30 subjects, 6 subjects, 4 subjects, 14 subjects, 25 subjects, and 7 subjects), and memantine (142 subjects total; 43 subjects, 7 subjects, 7 subjects, 16 subjects, 45 subjects, and 24 subjects). Table 21 shows the ApoE ε4 carrier status in the treatment groups.

Table 21. ApoE ε4 carrier status in the treatment groups (FAS)

	Placebo	Lecanemab				
		2.5 mg/kg biweekly	5 mg/kg monthly	5 mg/kg biweekly	10 mg/kg monthly	10 mg/kg biweekly
ApoE ε4 carrier	71.0 (169)	73.1 (38)	77.1 (37)	91.0 (81)	88.6 (218)	30.3 (46)
Homozygous	16.8 (40)	9.6 (5)	22.9 (11)	15.7 (14)	23.6 (58)	5.3 (8)
Heterozygous	54.2 (129)	63.5 (33)	54.2 (26)	75.3 (67)	65.0 (160)	25.0 (38)
ApoE ε4 non-carrier	29.0 (69)	26.9 (14)	22.9 (11)	9.0 (8)	11.4 (28)	69.7 (106)

% (n)

Table 22 shows the change from baseline in Alzheimer's Disease Composite Score (ADCOMS)[27] at Month 12, the primary efficacy endpoint. In a Bayesian analysis (normal dynamic linear model),[28] the primary analysis for the primary endpoint, the 10 mg/kg biweekly regimen was identified as the dose regimen with at least 90% of the maximum effective dose treatment effect (ED_{90}). The estimation result for the analysis was that the lecanemab 10 mg/kg biweekly regimen had a 64% probability of being superior to placebo by a clinically meaningful difference (defined as the difference calculated to slow progression of decline in ADCOMS by ≥25% compared with placebo after 1 year of lecanemab treatment), which did not meet the prespecified success criterion of >80%.

[26] Subjects who had been on the medication before and at the start of study drug treatment, or subjects who started taking the medication at the start of or after the start of study drug treatment and continued until 30 days after the final dose of study drug.

[27] The ADCOMS is an assessment scale system consisting of a total of 12 items from CDR (all 6 items), ADAS-Cog14 (4 of the items), and MMSE (2 of the items), with values ranging from 0 to 1.97. The ADCOMS, which was developed by the applicant, is a composite scale system sensitive to progression of clinical symptoms and therapeutic effect in patients with MCI.

[28] Subjects who had not been on ChE inhibitors and memantine at randomization were treated as censored at the time of initiation of ChE inhibitors or memantine after randomization. Subjects who had been on a stable dose of ChE inhibitors or memantine at randomization were treated as censored at the time of dose adjustment of the ChE inhibitor or memantine after randomization. Data after the time of censoring were imputed with data until censoring and by a Bayesian approach.

Table 22. Change from baseline in ADCOMS at Month 12 (FAS)

	Placebo	Lecanemab				
		2.5 mg/kg biweekly	5 mg/kg Monthly	5 mg/kg biweekly	10 mg/kg Monthly	10 mg/kg biweekly
Baseline[a]	N = 238 0.37 ± 0.17	N = 52 0.39 ± 0.20	N = 48 0.40 ± 0.17	N = 89 0.39 ± 0.16	N = 246 0.37 ± 0.15	N = 152 0.37 ± 0.15
Month 12[a]	N = 206 0.46 ± 0.25	N = 42 0.53 ± 0.30	N = 45 0.49 ± 0.25	N = 69 0.48 ± 0.22	N = 181 0.44 ± 0.22	N = 98 0.46 ± 0.23
Change from baseline[a]	0.10 ± 0.16	0.15 ± 0.20	0.11 ± 0.17	0.10 ± 0.14	0.08 ± 0.16	0.08 ± 0.14

a, Mean ± standard deviation

The tables below show the results for the secondary efficacy endpoints: the change from baseline in ADCOMS at Month 18 (Table 23), change from baseline in Clinical Dementia Rating-Sum of Boxes (CDR-SB)[29)] and Alzheimer's Disease Assessment Scale-Cognitive subscale with 14 tasks (ADAS-Cog14)[30)] at Months 12 and 18 (Table 24), and change from baseline in amyloid PET standard uptake value ratio (SUVr)[31)] at Months 12 and 18 (Table 25).

Table 23. Change from baseline in ADCOMS at Month 18 (FAS)

	Placebo	Lecanemab				
		2.5 mg/kg biweekly	5 mg/kg monthly	5 mg/kg biweekly	10 mg/kg monthly	10 mg/kg biweekly
Baseline[a]	N = 238 0.37 ± 0.17	N = 52 0.39 ± 0.20	N = 48 0.40 ± 0.17	N = 89 0.39 ± 0.16	N = 246 0.37 ± 0.15	N = 152 0.37 ± 0.15
Month 18[a]	N = 184 0.52 ± 0.27	N = 37 0.55 ± 0.32	N = 39 0.48 ± 0.25	N = 64 0.55 ± 0.27	N = 163 0.50 ± 0.27	N = 85 0.49 ± 0.26
Change from baseline[a]	0.16 ± 0.20	0.17 ± 0.23	0.12 ± 0.19	0.17 ± 0.21	0.14 ± 0.22	0.12 ± 0.18

a, Mean ± standard deviation

29) The CDR is a clinical assessment scale that describes 5 degrees of impairment on each of a total of 6 categories, 3 categories from the cognition domain (memory, orientation, judgment and problem solving) and 3 categories from the function domain (community affairs, home and hobbies, and personal care). The rating ranges from 0 (none), 0.5 (questionable), 1 (mild), 2 (moderate), and 3 (severe). The CDR-SB sums each of the domain scores.

30) The ADAS-Cog14 is a structured assessment scale that evaluates memory (word recall, delayed word recall, and word recognition), reasoning (following commands), language (naming, comprehension), orientation, ideational praxis (placing letter in envelope), and constructional praxis (copying geometric designs). Spoken language, language comprehension, word finding difficulty, ability to remember test instructions, maze, and number cancellation are also rated, and the rating is scored from 0 to 90 points.

31) To subjects participating in the amyloid PET substudy, florbetapir (^{18}F) or flutemetamol (^{18}F) was used. However, only data from subjects receiving florbetapir (^{18}F) were used for the calculation of summary statistics and other analyses on PET scans. The whole cerebellum was used as the reference region.

Table 24. Change from baseline in CDR-SB and ADAS-Cog14 at Months 12 and 18 (FAS)

		Placebo	Lecanemab				
			2.5 mg/kg biweekly	5 mg/kg monthly	5 mg/kg biweekly	10 mg/kg monthly	10 mg/kg biweekly
CDR-SB	Baseline[a]	N = 238 2.89 ± 1.45	N = 52 2.98 ± 1.58	N = 48 2.94 ± 1.42	N = 89 3.03 ± 1.31	N = 246 2.91 ± 1.32	N = 152 2.97 ± 1.40
	Month 12[a]	N = 207 3.51 ± 1.99	N = 42 4.08 ± 2.46	N = 45 3.86 ± 2.15	N = 72 3.70 ± 1.93	N = 182 3.48 ± 1.92	N = 99 3.58 ± 1.95
	Change from baseline[a]	0.73 ± 1.40	1.18 ± 1.91	0.99 ± 1.37	0.75 ± 1.45	0.59 ± 1.53	0.46 ± 1.38
	Month 18[a]	N = 185 4.01 ± 2.26	N = 38 4.24 ± 2.76	N = 40 3.91 ± 2.23	N = 70 4.24 ± 2.52	N = 166 4.01 ± 2.44	N = 91 4.13 ± 2.43
	Change from baseline[a]	1.27 ± 1.78	1.37 ± 2.17	1.23 ± 1.78	1.26 ± 2.01	1.10 ± 2.03	1.04 ± 1.98
ADAS-Cog14	Baseline[a]	N = 237 22.56 ± 7.66	N = 52 22.72 ± 8.05	N = 47 22.94 ± 7.74	N = 89 22.75 ± 6.70	N = 246 21.90 ± 7.30	N = 152 22.06 ± 7.67
	Month 12[a]	N = 205 24.43 ± 10.60	N = 42 25.75 ± 12.20	N = 45 25.38 ± 10.64	N = 71 24.09 ± 7.22	N = 180 23.17 ± 10.08	N = 99 24.54 ± 10.48
	Change from baseline[a]	2.25 ± 6.24	2.93 ± 6.70	2.34 ± 7.14	2.04 ± 4.87	1.79 ± 5.86	1.87 ± 6.26
	Month 18[a]	N = 182 25.68 ± 11.39	N = 37 26.87 ± 12.68	N = 39 25.97 ± 10.40	N = 64 25.79 ± 9.26	N = 163 25.21 ± 11.30	N = 86 24.53 ± 10.80
	Change from baseline[a]	3.75 ± 7.37	4.17 ± 7.17	3.50 ± 6.85	3.57 ± 6.74	3.91 ± 7.59	2.64 ± 7.22

a, Mean ± standard deviation

Table 25. Change from baseline in amyloid PET SUVr at Months 12 and 18 (PD analysis set)

	Placebo	Lecanemab				
		2.5 mg/kg biweekly	5 mg/kg monthly	5 mg/kg biweekly	10 mg/kg monthly	10 mg/kg biweekly
Baseline[a]	N = 98 1.40 ± 0.16	N = 28 1.41 ± 0.11	N = 27 1.42 ± 0.17	N = 27 1.40 ± 0.12	N = 88 1.42 ± 0.18	N = 44 1.37 ± 0.16
Month 12[a]	N = 96 1.40 ± 0.16	N = 27 1.36 ± 0.11	N = 27 1.35 ± 0.18	N = 25 1.25 ± 0.14	N = 88 1.25 ± 0.14	N = 43 1.11 ± 0.13
Change from baseline[a]	0.00 ± 0.09	−0.06 ± 0.08	−0.07 ± 0.10	−0.15 ± 0.08	−0.18 ± 0.12	−0.26 ± 0.13
Month 18[a]	N = 88 1.40 ± 0.16	N = 23 1.33 ± 0.13	N = 23 1.32 ± 0.16	N = 24 1.22 ± 0.15	N = 82 1.20 ± 0.13	N = 37 1.07 ± 0.12
Change from baseline[a]	0.01 ± 0.10	−0.08 ± 0.07	−0.13 ± 0.10	−0.19 ± 0.11	−0.22 ± 0.13	−0.30 ± 0.14

a, Mean ± standard deviation

Table 26 shows the incidence of adverse events.

Table 26. Incidence of adverse events (Safety analysis set)

	Placebo (N = 245)	Lecanemab				
		2.5 mg/kg biweekly (N = 52)	5 mg/kg monthly (N = 51)	5 mg/kg biweekly (N = 92)	10 mg/kg monthly (N = 253)	10 mg/kg biweekly (N = 161)
All adverse events	88.2 (216)	88.5 (46)	94.1 (48)	88.0 (81)	94.1 (238)	86.3 (139)
Main events[a]						
Infusion related reaction	3.3 (8)	5.8 (3)	7.8 (4)	12.0 (11)	23.3 (59)	19.9 (32)
Headache	10.2 (25)	17.3 (9)	7.8 (4)	18.5 (17)	17.0 (43)	14.3 (23)
Upper respiratory tract infection	16.7 (41)	13.5 (7)	13.7 (7)	10.9 (10)	9.1 (23)	11.8 (19)
Urinary tract infection	13.5 (33)	9.6 (5)	9.8 (5)	18.5 (17)	9.9 (25)	10.6 (17)
Fall	13.1 (32)	5.8 (3)	11.8 (6)	14.1 (13)	8.7 (22)	10.6 (17)
Amyloid related imaging abnormality-oedema/effusion	0.8 (2)	1.9 (1)	2.0 (1)	3.3 (3)	9.9 (25)	9.9 (16)
Cough	4.9 (12)	1.9 (1)	3.9 (2)	4.3 (4)	4.3 (11)	8.7 (14)
Dizziness	7.8 (19)	7.7 (4)	0 (0)	10.9 (10)	3.6 (9)	8.7 (14)
Nasopharyngitis	11.4 (28)	5.8 (3)	13.7 (7)	9.8 (9)	7.5 (19)	8.1 (13)
Diarrhoea	4.9 (12)	9.6 (5)	13.7 (7)	13.0 (12)	6.3 (16)	8.1 (13)
Back pain	9.8 (24)	7.7 (4)	11.8 (6)	4.3 (4)	7.9 (20)	6.8 (11)
Cerebral microhaemorrhage	4.9 (12)	3.8 (2)	13.7 (7)	13.0 (12)	8.7 (22)	6.2 (10)
Fatigue	6.1 (15)	7.7 (4)	2.0 (1)	7.6 (7)	6.7 (17)	5.6 (9)
Arthralgia	6.9 (17)	0 (0)	7.8 (4)	6.5 (6)	4.7 (12)	4.3 (7)
Contusion	2.9 (7)	3.8 (2)	9.8 (5)	6.5 (6)	4.3 (11)	4.3 (7)
Hypertension	5.3 (13)	1.9 (1)	2.0 (1)	3.3 (3)	4.0 (10)	4.3 (7)
Sinusitis	3.3 (8)	1.9 (1)	9.8 (5)	1.1 (1)	3.6 (9)	4.3 (7)
Nausea	4.1 (10)	1.9 (1)	7.8 (4)	8.7 (8)	5.9 (15)	3.7 (6)
Anxiety	6.1 (15)	1.9 (1)	5.9 (3)	4.3 (4)	4.0 (10)	3.7 (6)
Depression	5.3 (13)	1.9 (1)	5.9 (3)	6.5 (6)	5.1 (13)	3.1 (5)
Agitation	1.6 (4)	3.8 (2)	3.9 (2)	5.4 (5)	2.8 (7)	3.1 (5)
Skin abrasion	3.3 (8)	0 (0)	2.0 (1)	1.1 (1)	5.1 (13)	2.5 (4)
Bronchitis	6.1 (15)	0 (0)	0 (0)	2.2 (2)	3.6 (9)	2.5 (4)
Procedural pain	1.6 (4)	5.8 (3)	3.9 (2)	2.2 (2)	1.6 (4)	2.5 (4)
Pain in extremity	4.1 (10)	1.9 (1)	3.9 (2)	7.6 (7)	3.2 (8)	1.9 (3)
Influenza	0.8 (2)	0 (0)	2.0 (1)	5.4 (5)	2.8 (7)	1.9 (3)
Muscle spasms	2.0 (5)	1.9 (1)	11.8 (6)	0 (0)	2.0 (5)	1.9 (3)
Basal cell carcinoma	2.9 (7)	7.7 (4)	3.9 (2)	6.5 (6)	1.6 (4)	1.9 (3)
Vomiting	3.7 (9)	3.8 (2)	7.8 (4)	7.6 (7)	4.0 (10)	1.2 (2)
Insomnia	2.9 (7)	5.8 (3)	5.9 (3)	3.3 (3)	2.8 (7)	1.2 (2)
Hypotension	2.0 (5)	3.8 (2)	5.9 (3)	2.2 (2)	2.0 (5)	1.2 (2)
Superficial siderosis of central nervous system	0.4 (1)	0 (0)	2.0 (1)	5.4 (5)	2.8 (7)	0.6 (1)
Drug eruption	0.4 (1)	5.8 (3)	0 (0)	2.2 (2)	1.6 (4)	0.6 (1)
Squamous cell carcinoma of skin	1.6 (4)	5.8 (3)	2.0 (1)	2.2 (2)	1.2 (3)	0.6 (1)
Erythema	0.8 (2)	0 (0)	5.9 (3)	1.1 (1)	0.4 (1)	0.6 (1)

% (n)

a, Adverse events occurring in ≥5% of subjects in any group

There were 2 deaths in the placebo group (acute respiratory failure, sarcoma), 2 in the lecanemab 2.5 mg/kg biweekly group (brain neoplasm, cardiac arrest), 1 in the 5 mg/kg biweekly group (multiple organ dysfunction syndrome), and 2 in the 10 mg/kg monthly group (spinal cord injury, respiratory failure). A causal relationship to lecanemab could not be ruled out for brain neoplasm. Other serious adverse events are presented in Table 27. Among these serious adverse events, a causal relationship to the study drug could not be ruled out for amyloid related imaging abnormalities, cerebral microhaemorrhage, syncope (1 subject in the placebo group), and transient ischaemic attack (1 subject each in the lecanemab 10 mg/kg monthly and 10 mg/kg biweekly groups).

Table 27. Incidence of serious adverse events except for death (Safety analysis set)

	Placebo (N = 245)	Lecanemab				
		2.5 mg/kg biweekly (N = 52)	5 mg/kg monthly (N = 51)	5 mg/kg biweekly (N = 92)	10 mg/kg monthly (N = 253)	10 mg/kg biweekly (N = 161)
Serious adverse events	17.6 (43)	19.2 (10)	7.8 (4)	17.4 (16)	12.3 (31)	15.5 (25)
Main events[a]						
Amyloid related imaging abnormality-oedema/effusion	0 (0)	0 (0)	0 (0)	0 (0)	0.4 (1)	1.9 (3)
Non-cardiac chest pain	0 (0)	0 (0)	0 (0)	0 (0)	0.8 (2)	1.2 (2)
Pulmonary embolism	0 (0)	0 (0)	0 (0)	0 (0)	0.4 (1)	1.2 (2)
Arthralgia	0 (0)	0 (0)	0 (0)	1.1 (1)	0 (0)	1.2 (2)
Cerebral microhaemorrhage	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1.2 (2)
Dyspnoea	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1.2 (2)
Transient ischaemic attack	0.4 (1)	0 (0)	3.9 (2)	0 (0)	0.4 (1)	0.6 (1)
Syncope	1.2 (3)	0 (0)	0 (0)	1.1 (1)	0.4 (1)	0.6 (1)
Subdural haematoma	0.8 (2)	1.9 (1)	0 (0)	0 (0)	0 (0)	0.6 (1)
Fall	1.6 (4)	0 (0)	0 (0)	0 (0)	0.4 (1)	0 (0)
Osteoarthritis	1.6 (4)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Pulmonary mass	0 (0)	3.8 (2)	0 (0)	0 (0)	0 (0)	0 (0)

% (n)
a, Adverse events occurring in ≥2 subjects in any group

Table 28 shows the incidence of adverse events leading to treatment discontinuation. A causal relationship to the study drug could not be ruled out for amyloid related imaging abnormalities, infusion related reaction, cerebral microhaemorrhage, superficial siderosis of central nervous system, atrial fibrillation (1 subject in the lecanemab 10 mg/kg monthly group), and confusional state (2 subjects in the 10 mg/kg monthly group).

Table 28. Incidence of adverse events leading to study drug treatment discontinuation (Safety analysis set)

	Placebo (N = 245)	Lecanemab				
		2.5 mg/kg biweekly (N = 52)	5 mg/kg monthly (N = 51)	5 mg/kg biweekly (N = 92)	10 mg/kg monthly (N = 253)	10 mg/kg biweekly (N = 161)
Adverse events leading to study drug treatment discontinuation	6.1 (15)	13.5 (7)	7.8 (4)	10.9 (10)	18.6 (47)	14.9 (24)
Main events[a]						
Amyloid related imaging abnormality-oedema/effusion	0.4 (1)	1.9 (1)	2.0 (1)	3.3 (3)	9.9 (25)	9.9 (16)
Infusion related reaction	0.8 (2)	0 (0)	0 (0)	0 (0)	2.0 (5)	2.5 (4)
Cerebral microhaemorrhage	0 (0)	0 (0)	3.9 (2)	0 (0)	3.2 (8)	1.2 (2)
Atrial fibrillation	0 (0)	1.9 (1)	0 (0)	0 (0)	0.8 (2)	1.2 (2)
Superficial siderosis of central nervous system	0 (0)	0 (0)	2.0 (1)	3.3 (3)	2.0 (5)	0.6 (1)
Confusional state	0.4 (1)	0 (0)	0 (0)	0 (0)	0.8 (2)	0 (0)

% (n)
a, Adverse events occurring in ≥2 subjects in any group

Japanese population

All 34 subjects enrolled in the Core study (10 subjects [placebo], 1 subject [lecanemab 2.5 mg/kg biweekly], 6 subjects [5 mg/kg biweekly], 12 subjects [10 mg/kg monthly], and 5 subjects [10 mg/kg biweekly]; the same applies hereinafter for the order of assigned groups) received the study drug and were included in the safety analysis set and FAS. Five subjects discontinued from the study (0 subjects, 1 subject, 1 subject, 1 subject, and 2 subjects), and the reasons for discontinuation were “adverse events” (1 subject in the 10 mg/kg biweekly

group), "subject's choice" (1 subject in the 10 mg/kg biweekly group), "withdrawal of consent" (1 subject in the 5 mg/kg biweekly group), and "other reasons" (1 subject in the 2.5 mg/kg biweekly group, 1 subject in the 10 mg/kg monthly group). Concomitant AD medications[26] were donepezil (19 subjects total; 5 subjects, 1 subject, 6 subjects, 4 subjects, and 3 subjects), galantamine (5 subjects total; 1 subject, 0 subjects, 0 subjects, 3 subjects, and 1 subject), rivastigmine (5 subjects total; 1 subject, 0 subjects, 0 subjects, 3 subjects, and 1 subject). Table 29 shows the ApoE ε4 carrier status in the treatment groups.

Table 29. ApoE ε4 carrier status in the treatment groups (FAS, Japanese population)

	Placebo	Lecanemab				
		2.5 mg/kg biweekly	5 mg/kg monthly	5 mg/kg biweekly	10 mg/kg monthly	10 mg/kg biweekly
ApoE ε4 carrier	40.0 (4)	100 (1)	—	100 (6)	100 (12)	0 (0)
Homozygous	10.0 (1)	0 (0)	—	0 (0)	41.7 (5)	0 (0)
Heterozygous	30.0 (3)	100 (1)	—	100 (6)	58.3 (7)	0 (0)
ApoE ε4 non-carrier	60.0 (6)	0 (0)	—	0 (0)	0 (0)	100 (5)

% (n); "—," Not allocated

Table 30 shows the results for the primary efficacy endpoint (change from baseline in ADCOMS at Month 12).

Table 30. Change from baseline in ADCOMS at Month 12 (FAS, Japanese population)

	Placebo	Lecanemab				
		2.5 mg/kg biweekly	5 mg/kg monthly	5 mg/kg biweekly	10 mg/kg monthly	10 mg/kg biweekly
Baseline[a]	N = 10 0.39 ± 0.11	N = 1 0.65[b]	—	N = 6 0.49 ± 0.21	N = 12 0.38 ± 0.13	N = 5 0.37 ± 0.09
Month 12[a]	N = 10 0.54 ± 0.23	N = 1 0.35[b]	—	N = 6 0.63 ± 0.24	N = 11 0.51 ± 0.25	N = 5 0.47 ± 0.17
Change from baseline[a]	0.16 ± 0.14	−0.30[b]	—	0.14 ± 0.14	0.12 ± 0.20	0.10 ± 0.14

"—," Not allocated

a, Mean ± standard deviation (except for b); b, Individual value

The tables below show the results for the secondary efficacy endpoints in Japanese subjects: the change from baseline in ADCOMS at Month 18 (Table 31) and change from baseline in CDR-SB and ADAS-Cog14 at Months 12 and 18 (Table 32). The change from baseline in amyloid PET SUVr was not studied in Japanese subjects because they were not included in the PD analysis set.

Table 31. Change from baseline in ADCOMS at Month 18 (FAS, Japanese population)

	Placebo	Lecanemab				
		2.5 mg/kg biweekly	5 mg/kg monthly	5 mg/kg biweekly	10 mg/kg monthly	10 mg/kg biweekly
Baseline[a]	N = 10 0.39 ± 0.11	N = 1 0.65[b]	—	N = 6 0.49 ± 0.21	N = 12 0.38 ± 0.13	N = 5 0.37 ± 0.09
Month 18[a]	N = 10 0.64 ± 0.29	N = 1 0.38[b]	—	N = 5 0.76 ± 0.32	N = 10 0.50 ± 0.26	N = 3 0.45 ± 0.22
Change from baseline[a]	0.25 ± 0.22	−0.27[b]	—	0.23 ± 0.20	0.13 ± 0.22	0.09 ± 0.22

"—," Not allocated

a, Mean ± standard deviation (except for b); b, individual value

Table 32. Change from baseline in CDR-SB and ADAS-Cog14 at Months 12 and 18 (FAS, Japanese population)

		Placebo	Lecanemab				
			2.5 mg/kg biweekly	5 mg/kg monthly	5 mg/kg biweekly	10 mg/kg monthly	10 mg/kg biweekly
CDR-SB	Baseline[a]	N = 10 2.50 ± 0.85	N = 1 5.50[b]	—	N = 6 3.58 ± 1.69	N = 12 2.63 ± 1.23	N = 5 2.90 ± 0.42
	Month 12[a]	N = 10 4.05 ± 1.92	N = 1 3.00[b]	—	N = 6 4.58 ± 2.33	N = 11 3.73 ± 2.17	N = 5 3.40 ± 0.89
	Change from baseline[a]	1.55 ± 1.52	−2.50[b]	—	1.00 ± 1.23	1.00 ± 1.79	0.50 ± 1.23
	Month 18[a]	N = 10 4.65 ± 2.40	N = 1 3.00[b]	—	N = 5 5.70 ± 3.38	N = 11 3.73 ± 2.22	N = 4 3.63 ± 0.85
	Change from baseline[a]	2.15 ± 2.20	−2.50[b]	—	1.90 ± 2.61	1.00 ± 1.92	0.63 ± 1.03
ADAS-Cog14	Baseline[a]	N = 10 23.00 ± 5.60	N = 1 25.33[b]	—	N = 6 26.94 ± 5.44	N = 12 24.64 ± 4.61	N = 5 23.87 ± 4.65
	Month 12[a]	N = 10 26.90 ± 9.13	N = 1 28.33[b]	—	N = 6 26.06 ± 5.00	N = 11 24.76 ± 8.01	N = 5 27.67 ± 7.69
	Change from baseline[a]	3.90 ± 6.21	3.00[b]	—	−0.89 ± 4.35	0.48 ± 5.04	3.80 ± 4.28
	Month 18[a]	N = 10 30.77 ± 11.80	N = 1 34.00[b]	—	N = 5 29.60 ± 6.03	N = 10 25.67 ± 9.41	N = 3 28.56 ± 12.04
	Change from baseline[a]	7.77 ± 9.52	8.67[b]	—	1.60 ± 3.75	1.87 ± 6.26	6.67 ± 7.84

"—," Not allocated
a, Mean ± standard deviation (except for b); b, Individual value

Table 33 shows the incidence of adverse events.

Table 33. Incidence of adverse events (Safety analysis set, Japanese population)

	Placebo (N = 10)	Lecanemab				
		2.5 mg/kg biweekly (N = 1)	5 mg/kg monthly (N = 0)	5 mg/kg biweekly (N = 6)	10 mg/kg monthly (N = 12)	10 mg/kg biweekly (N = 5)
Overall incidence	80.0 (8)	100 (1)	—	100 (6)	83.3 (10)	80.0 (4)
Main events[a]						
Nasopharyngitis	10.0 (1)	0 (0)	—	16.7 (1)	25.0 (3)	60.0 (3)
Back pain	10.0 (1)	0 (0)	—	0 (0)	16.7 (2)	20.0 (1)
Toothache	0 (0)	0 (0)	—	0 (0)	16.7 (2)	20.0 (1)
Hypertension	10.0 (1)	100 (1)	—	0 (0)	16.7 (2)	0 (0)
Lacunar infarction	0 (0)	0 (0)	—	0 (0)	16.7 (2)	0 (0)
Urinary tract infection	0 (0)	0 (0)	—	33.3 (2)	8.3 (1)	0 (0)
Arthralgia	20.0 (2)	0 (0)	—	0 (0)	0 (0)	0 (0)

% (n); "—," Not allocated
a, Adverse events occurring in ≥2 subjects in any group

There were no deaths. Other serious adverse events occurred in 1 subject in the placebo group (femur fracture) and 2 subjects in the 5 mg/kg biweekly group (enterocolitis, altered state of consciousness), and a causal relationship to the study drug was denied for all these events.

An adverse event led to treatment discontinuation in 1 subject in the 10 mg/kg biweekly group (ARIA-E), for which a causal relationship to the study drug could not be ruled out.

(b) Open-label extension phase

All subjects who entered OLE after the gap period were to receive intravenous doses of lecanemab 10 mg/kg biweekly under open-label conditions.

Key eligibility criteria were patients who had been enrolled in the Core study and met the following conditions.

- Patients who completed Visit 42 of the Core study (Week 79) or discontinued from the Core study for any of the following reasons:
  - Occurrence of ARIA-E
  - Occurrence of ARIA-H (superficial siderosis, cerebral hemorrhage, or symptomatic cerebral microhemorrhage)
  - Use of medications[32] which are not prohibited in the OLE but were prohibited or restricted during the Core study
  - ApoE ε4 carriers who were receiving lecanemab 10 mg/kg biweekly treatment
  - Reasons for discontinuation unrelated to prohibited medications, including onset of adverse events determined to be unrelated to the study drug and not severe or life-threatening
- The brain MRI scan at baseline of OLE indicates no critical pathological findings such as the following:
  - A cerebral hemorrhage >10 mm at the greatest diameter (symptomatic or worsened from the Core study)
  - Superficial siderosis (symptomatic or worsened from the Core study)
  - Vasogenic edema (severe or symptomatic)
  - Aneurysm, vascular malformation, infective lesions
  - Multiple lacunar infarction, stroke involving a major vascular territory, severe small vessel, or white matter disease
  - Space occupying lesions or brain tumors (however, lesions diagnosed as meningiomas or arachnoid cysts <1 cm at the greatest diameter need not be exclusionary)

In subjects in whom ARIA-E or ARIA-H was observed, treatment with the study drug was to be continued or discontinued according to the criteria below (Table 34). The prophylactic medications before study drug treatment was equivalent to that implemented in the Core study.

Table 34. Criteria for study drug treatment continuation or discontinuation for ARIA-E or ARIA-H

	Criteria
ARIA-E	**If asymptomatic and mild or moderate ARIA-E on MRI is observed** • If ARIA-E has not progressed to severe on MRI and remains asymptomatic, continue study drug treatment. • Approximately 30 days and 90 days after the visit in which the sign was first noted on MRI, perform safety evaluation (MRI scan) at scheduled or unscheduled visits. In Japan, when mild ARIA-E is noted on MRI and is asymptomatic, if it has not progressed to moderate or severe ARIA-E, and remains asymptomatic, study drug treatment is to be continued. **If symptomatic ARIA-E or severe ARIA-E on MRI is observed** • Interrupt study treatment until ARIA-E resolves on MRI and follow up the subject until ARIA-E resolves (including resolution of symptoms if present). • Approximately 30 days and 90 days after the visit in which symptomatic ARIA-E or severe ARIA-E is first noted on MRI, perform safety evaluation (MRI scan) at scheduled or unscheduled visits. Thereafter, perform safety

[32] Immunoglobulin therapy, biological products, and anticoagulants (permitted only for short-term treatment [4 weeks]; however, study drug treatment was to be interrupted during anticoagulant therapy).

	Criteria
	evaluation (MRI scan) at scheduled or unscheduled visits approximately every 30 days until ARIA-E resolves both on MRI and clinically. • Resumption of study drug treatment following identification of symptomatic ARIA-E is allowed no more than twice. If symptomatic ARIA-E occurs for a third time, discontinue the study drug treatment. In Japan, when symptomatic ARIA-E or moderate or severe ARIA-E is noted on MRI, study drug treatment may be continued or discontinued according to the following: • Interrupt study treatment until ARIA-E resolves on MRI and follow up the subject until ARIA-E resolves (including resolution of symptoms if present). • Approximately 30 days and 90 days after the visit in which symptomatic ARIA-E or moderate or severe ARIA-E was first noted on MRI, perform safety evaluation (MRI scan) at scheduled or unscheduled visits. Thereafter, perform safety evaluation (MRI scan) at scheduled or unscheduled visits approximately every 30 days until ARIA-E resolves on MRI and clinically. • During study treatment interruption due to symptomatic ARIA-E or moderate or severe ARIA-E on MRI, these subjects should visit study sites as scheduled for evaluation. • Resumption of study drug treatment following identification of symptomatic ARIA-E or moderate or severe ARIA-E on MRI is allowed no more than twice. If ARIA-E as described above appears for a third time, discontinue the study drug treatment.
ARIA-H	**If asymptomatic cerebral microhemorrhages (≤10 microhemorrhages) are observed** • No action is needed regarding study drug treatment or follow-up. **If asymptomatic and multiple cerebral microhemorrhages (>10 microhemorrhages), superficial siderosis, or sporadic cerebral hemorrhages (>10 mm at the greatest diameter) are observed** • No action needs to be taken regarding study drug treatment. • Approximately 30 days after the visit in which the sign was first noted on MRI (asymptomatic ARIA-H), perform safety evaluation (MRI scan) at an unscheduled visit. Thereafter, perform safety evaluation (MRI scan) at scheduled or unscheduled visits approximately every 30 days until asymptomatic ARIA-H stabilizes on MRI. **If symptomatic ARIA-H (symptomatic cerebral microhemorrhage, symptomatic superficial siderosis, or symptomatic cerebral hemorrhage) is observed** • Interrupt study treatment until ARIA-H stabilizes on MRI and becomes asymptomatic. • Approximately 30 days after the visit in which the sign (ARIA-H) was first noted on MRI, perform safety evaluation (MRI scan) at a scheduled or unscheduled visit. Thereafter, perform safety evaluation (MRI scan) at scheduled or unscheduled visits approximately every 30 days until ARIA-H stabilizes on MRI and the patient becomes asymptomatic. Resumption of study drug treatment following identification of symptomatic ARIA-H is allowed no more than twice. If symptomatic ARIA-H appears for a third time, discontinue the study drug treatment.

All the 180 subjects enrolled received the study drug, and were included in the OLE Safety analysis set. Of subjects in the OLE Safety analysis set, 172 subjects had evaluable efficacy data at baseline and ≥1 timepoint post-study dose in the OLE phase, and were included in the OLE-FAS, which was the primary efficacy analysis set. The OLE PD analysis set comprised 102 subjects[33)] who had data that could be used to calculate ≥1 PD parameter. In the OLE, 82 subjects discontinued from the study, with common reasons for discontinuation being "subject's choice" (30 subjects), "withdrawal of consent" (24 subjects), and "adverse events" (8 subjects).

Four treatment groups were defined for the analyses of the OLE phase based on the treatment groups of the Core study (Table 35).

Table 35. Definitions of treatment groups in the OLE phase

OLE treatment group	Core study treatment group
Group A	Placebo
Group B	Lecanemab 2.5 mg/kg biweekly, 5 mg/kg monthly, and 5 mg/kg biweekly
Group C	lecanemab 10 mg/kg monthly
Group D	Lecanemab 10 mg/kg biweekly

33) The number of subjects who had amyloid PET data.

The change from OLE baseline in ADCOMS, CDR-SB, and ADAS-Cog14 over time (Table 36) and change from OLE baseline in amyloid PET SUVr over time (Table 37) are shown below.

Table 36. Change from OLE baseline in ADCOMS, CDR-SB, and ADAS-Cog14 over time (OLE-FAS)

		Group A (N = 42)	Group B (N = 35)	Group C (N = 58)	Group D (N = 37)
ADCOMS	OLE baseline[a]	N = 40 0.59 ± 0.32	N = 35 0.70 ± 0.36	N = 54 0.64 ± 0.36	N = 36 0.63 ± 0.41
	Change from OLE baseline				
	Month 6 of OLE[a]	N = 37 0.09 ± 0.14	N = 32 0.09 ± 0.14	N = 51 0.09 ± 0.16	N = 33 0.12 ± 0.20
	Month 12 of OLE[a]	N = 31 0.09 ± 0.19	N = 26 0.15 ± 0.19	N = 40 0.14 ± 0.16	N = 26 0.09 ± 0.16
	Month 24 of OLE[a]	N = 17 0.15 ± 0.18	N = 9 0.22 ± 0.24	N = 21 0.21 ± 0.20	N = 14 0.18 ± 0.18
CDR-SB	OLE baseline[a]	N = 42 4.69 ± 3.21	N = 35 5.27 ± 3.06	N = 58 5.34 ± 3.53	N = 37 5.00 ± 3.70
	Change from OLE baseline				
	Month 6 of OLE[a]	N = 40 0.98 ± 1.87	N = 34 0.97 ± 1.44	N = 58 0.95 ± 1.64	N = 35 0.97 ± 2.33
	Month 12 of OLE[a]	N = 36 1.13 ± 2.13	N = 31 1.85 ± 2.49	N = 48 1.85 ± 2.22	N = 29 0.91 ± 1.98
	Month 24 of OLE[a]	N = 19 2.05 ± 3.10	N = 12 3.58 ± 3.64	N = 23 2.02 ± 2.16	N = 16 1.94 ± 2.10
ADAS-Cog14	OLE baseline[a]	N = 40 33.40 ± 13.49	N = 34 37.85 ± 13.97	N = 53 34.21 ± 13.46	N = 34 32.46 ± 13.79
	Change from OLE baseline				
	Month 6 of OLE[a]	N = 36 1.73 ± 5.63	N = 30 1.77 ± 3.98	N = 50 1.47 ± 4.58	N = 32 4.00 ± 5.44
	Month 12 of OLE[a]	N = 31 3.64 ± 7.39	N = 23 1.67 ± 4.16	N = 41 3.49 ± 4.15	N = 25 2.72 ± 4.41
	Month 24 of OLE[a]	N = 16 6.73 ± 8.75	N = 8 4.50 ± 9.75	N = 20 6.02 ± 6.44	N = 16 5.48 ± 5.89

a, Mean ± standard deviation

Table 37. Change from OLE baseline in amyloid PET SUVr (OLE PD analysis set)

	Group A (N = 27)	Group B (N = 19)	Group C (N = 34)	Group D (N = 22)
OLE baseline[a]	N = 22 1.37 ± 0.18	N = 17 1.27 ± 0.17	N = 31 1.22 ± 0.15	N = 21 1.08 ± 0.13
Change from OLE baseline				
Month 6 of OLE[a]	N = 11 −0.25 ± 0.07	N = 7 −0.09 ± 0.04	N = 11 −0.08 ± 0.05	N = 10 −0.02 ± 0.04
Month 12 of OLE[a]	N = 15 −0.27 ± 0.16	N = 11 −0.14 ± 0.11	N = 23 −0.13 ± 0.12	N = 17 −0.03 ± 0.06
Month 24 of OLE[a]	N = 7 −0.31 ± 0.20	N = 6 −0.20 ± 0.17	N = 14 −0.16 ± 0.10	N = 10 −0.08 ± 0.09

a, Mean ± standard deviation

Table 38 shows the incidence of adverse events.

Table 38. Incidence of adverse events (OLE Safety analysis set)

	Groups A to D (N = 180)
Overall incidence	95.0 (171)
Main events[a]	
Fall	22.2 (40)
Infusion related reaction	20.6 (37)
Urinary tract infection	15.0 (27)
Amyloid related imaging abnormality-microhaemorrhages and haemosiderin deposits	13.3 (24)
Nasopharyngitis	10.0 (18)
Headache	8.9 (16)
Arthralgia	8.3 (15)
Upper respiratory tract infection	8.3 (15)
Amyloid related imaging abnormality-oedema/effusion	7.8 (14)
Anxiety	7.8 (14)
Hypertension	7.8 (14)
Back pain	7.2 (13)
COVID-19	6.7 (12)
Dizziness	6.7 (12)
Skin laceration	6.7 (12)
Contusion	6.1 (11)
Depression	6.1 (11)
Basal cell carcinoma	5.6 (10)
Nausea	5.6 (10)
Hypotension	5.0 (9)
Pyrexia	5.0 (9)
Vomiting	5.0 (9)

% (n)
a, Adverse events occurring in ≥5% of subjects

There were 3 deaths (metastases to central nervous system, cervical vertebral fracture, malignant neoplasm of unknown primary site/neuroendocrine carcinoma), and a causal relationship to the study drug was denied for all these events. Other serious adverse events occurred in 43 subjects. Serious adverse events occurring in ≥2 subjects were fall (4 subjects), cervical vertebral fracture (3 subjects), transient ischaemic attack (3 subjects), acute kidney injury (3 subjects), atrial fibrillation (2 subjects), chest discomfort (2 subjects), pneumonia (2 subjects), hip fracture (2 subjects), rib fracture (2 subjects), and mental status changes (2 subjects).

Adverse events led to treatment discontinuation of the study drug in 7 subjects (pancytopenia, cervical vertebral fracture, infusion related reaction, road traffic accident/subdural haemorrhage, breast cancer metastatic, malignant neoplasm of unknown primary site/neuroendocrine carcinoma, and aggression). Among these events, infusion related reaction was determined to be related to the study drug.

7.3 Global phase III study (Study 301, CTD 5.3.5.1.4 and 5.3.5.1.5 [ongoing since March 2019, data cut-off in April 2022])

A randomized, double-blind, parallel-group study was conducted at 235 study centers in Japan and other countries to evaluate if lecanemab was superior to placebo in terms of slowing disease progression in patients with early AD (target sample size, approximately 1,766 subjects[34]).

The duration of the Core study was 18 months after randomization. The Core study was followed by the OLE phase for up to 48 months. In the following sections, in addition to the results for the overall population, the results for the Japanese population are also described for the Core study, a phase important for the evaluation of efficacy and safety in Japanese patients.

(a) Core study

Subjects were enrolled so that approximately 70% of the overall randomized subjects were to be ApoE ε4 carriers. Patients were recruited so that more than half of the patient population comprised patients with MCI due to AD.

In the Core study, placebo or lecanemab 10 mg/kg was intravenously administered biweekly.

The key eligibility criteria were similar to those for Study 201 Core.[35]

In subjects who developed ARIA-E or ARIA-H, study drug treatment was to be continued or discontinued according to the following criteria (Table 39).

Table 39. Criteria for study drug treatment continuation or discontinuation for ARIA-E or ARIA-H

	Criteria
ARIA-E	**If asymptomatic and mild ARIA-E on MRI is observed** • If ARIA-E has not progressed to moderate or severe on MRI and remains asymptomatic, continue study drug treatment. • Approximately 30 days, 60 days, and 90 days after the visit in which the sign was first noted on MRI, perform safety evaluation (MRI scan) at scheduled or unscheduled visits even if ARIA-E has resolved, and thereafter, follow the evaluation schedule. **If symptomatic ARIA-E or moderate or severe ARIA-E on MRI is observed** • Throughout the period including Core and OLE, if it is the first or second symptomatic ARIA-E or moderate or severe ARIA-E on MRI, interrupt study treatment until ARIA-E resolves both on MRI and clinically. • Approximately 30 days and 90 days after the visit in which the sign was first noted on MRI, perform safety evaluation (MRI scan) at scheduled or unscheduled visits even if ARIA-E has resolved. Thereafter, perform safety evaluation (MRI scan) at scheduled or unscheduled visits approximately every 30 days until ARIA-E resolves both on MRI and clinically. • Resumption of study drug treatment following identification of symptomatic ARIA-E or moderate or severe ARIA-E on MRI is allowed no more than twice throughout the period including Core and OLE. If symptomatic ARIA-E

[34] The target sample size required for superiority testing for the primary endpoint with two-sided significance level of 0.05 and a statistical power of 90% was 783 subjects per group (total of 1,566 subjects) assuming the difference between lecanemab and placebo being −0.373, a standard deviation of 2.031, and a drop-out rate of 20% on the basis of data from Study 201. It became clear that approximately 200 subjects were unable to receive ≥3 consecutive doses of the study drug during the study due to coronavirus disease 2019 (COVID-19) pandemic. Accordingly, approximately 200 subjects were added for randomization based on the agreement with FDA to maintain the power of 90%, and the target sample size was changed to approximately 1,766 subjects (December 2020).

[35] Findings suggestive of positive amyloid load was evaluated by amyloid PET assessment of imaging agent uptake or by the ratio of t-tau/Aβ (1-42) in CSF.

	Criteria
	or moderate or severe ARIA-E on MRI occurs for a third time, discontinue the study drug treatment. **If severe ARIA-E associated with serious adverse event (SAE) is observed on MRI** • Discontinue study drug treatment and report as SAE. • Approximately 30 days and 90 days after the visit in which ARIA-E was first noted, perform safety evaluation (MRI scan) at scheduled or unscheduled visits even if ARIA-E has resolved. Thereafter, perform safety evaluation (MRI scan) at scheduled or unscheduled visits approximately every 30 days until ARIA-E resolves both on MRI and clinically.
ARIA-H	**If asymptomatic cerebral microhemorrhages (≤10 microhemorrhages) or asymptomatic superficial siderosis is observed** • No action is needed regarding study drug treatment or follow-up. **If sporadic cerebral hemorrhages (>10 mm at the greatest diameter), symptomatic cerebral microhemorrhages, or symptomatic superficial siderosis is observed** • Throughout the period including Core and OLE, if it is the first or second sporadic cerebral hemorrhage (>10 mm at the greatest diameter), symptomatic cerebral microhemorrhages, or symptomatic superficial siderosis, interrupt study treatment until stabilization on MRI and the patient becomes asymptomatic. • Approximately 30 days after the visit in which the sign was first noted on MRI, and thereafter, perform safety evaluation (MRI scan) at scheduled or unscheduled visits approximately every 30 days until ARIA-H stabilizes on MRI and the patient becomes asymptomatic. • Resumption of study drug treatment following identification of sporadic cerebral hemorrhages (>10 mm at the greatest diameter), symptomatic cerebral microhemorrhages, or symptomatic superficial siderosis is allowed no more than twice throughout the period including Core and OLE. If sporadic cerebral hemorrhages (>10 mm at the greatest diameter), symptomatic cerebral microhemorrhages, or symptomatic superficial siderosis occurs for a third time, discontinue the study drug treatment. **If multiple cerebral microhemorrhages (>10 microhemorrhages) are observed** • Throughout the period including Core and OLE, if it is the first episode of multiple cerebral microhemorrhages (>10 microhemorrhages), interrupt study treatment until stabilization on MRI and the patient becomes asymptomatic. • Approximately 30 days after the visit in which the sign was first noted on MRI, perform safety evaluation (MRI scan) at an unscheduled visit. Thereafter, perform safety evaluation (MRI scan) at scheduled or unscheduled visits approximately every 30 days until ARIA-H stabilizes on MRI and the patient becomes asymptomatic. • Resumption of study drug treatment following identification of multiple cerebral microhemorrhages (>10 microhemorrhages) is allowed only once throughout the period including Core and OLE. If new cerebral microhemorrhages are observed after resumption, discontinue the study drug treatment.

The use of concomitant symptomatic AD medications (ChE inhibitors and/or memantine) and prophylactic medications before study drug doses were equivalent to those implemented in Study 201 Core.

Overall population

All of the 1,795 randomized subjects[36] (897 subjects [placebo] and 898 subjects [lecanemab]) received the study drug and were included in the safety analysis set. Of the safety analysis set, 1,734 subjects (875 subjects [placebo] and 859 subjects [lecanemab]) who had evaluable data for the primary efficacy endpoint at baseline and ≥1 timepoint post-study dose were included in the FAS+, which was used as the primary efficacy analysis set for application in Japan.[37] The PD analysis set comprised 716 subjects[38] (353 subjects [placebo] and 363 subjects [lecanemab]) who had data that could be used to calculate ≥1 PD parameter. A total of 309 subjects (140 subjects [placebo] and 169 subjects [lecanemab]) discontinued from the study, with common reasons for discontinuation being "withdrawal of consent" (136 subjects total; 67 subjects [placebo] and 69 subjects

[36] Randomization was stratified by clinical subgroups (MCI due to AD or mild AD-D), use or non-use of symptomatic AD medications, ApoE ε4 carrier status (carrier or non-carrier), and geographical region.

[37] In Study 301, the FAS was additionally defined during the study as the primary analysis set for marketing application in the US, and the FAS excluded subjects who were randomized before the closure date of study centers at which study drug treatment was interrupted for ≥6 weeks (≥42 days, equivalent to 3 consecutive doses) during the period of the COVID-19 pandemic (from March 1, 2020 to July 31, 2020) from the initially designed primary analysis set.

[38] The number of subjects who had amyloid PET data.

[lecanemab]) and "adverse events" (79 subjects total; 28 subjects [placebo] and 51 subjects [lecanemab]). Concomitant symptomatic AD medications[39] were used in 915 subjects (468 subjects [placebo] and 447 subjects [lecanemab]). Table 40 shows the ApoE ε4 carrier status.

Table 40. ApoE ε4 carrier status in each group (FAS+)

ApoE ε4 carrier status	Placebo	Lecanemab
Carrier	68.6 (600)	68.9 (592)
Homozygous	15.1 (132)	15.8 (136)
Heterozygous	53.5 (468)	53.1 (456)
Non-carrier	31.4 (275)	31.1 (267)

% (n)

Table 41 shows the change from baseline in CDR-SB[29] at Month 18, the primary efficacy endpoint. The results demonstrated the superiority of lecanemab over placebo in slowing the decline in CDR-SB.

Table 41. Change from baseline in CDR-SB (FAS+)

	Placebo	Lecanemab
Baseline[a]	N = 875 3.22 ± 1.34	N = 859 3.17 ± 1.34
Month 18[a]	N = 757 4.64 ± 2.70	N = 714 4.22 ± 2.49
Change from baseline (MMRM)[b, c]	N = 757 1.66 ± 0.08	N = 714 1.21 ± 0.08
Adjusted mean difference between groups	—	−0.45
P-value for between group difference[b]	—	0.00005

a, Mean ± standard deviation

b, Analyzed with a mixed model for repeated measures (MMRM) with baseline value as the covariate, with treatment group, assessment visit, stratification factors at randomization (clinical subgroup [MCI due to AD or mild AD-D], use/non-use of symptomatic AD medications, ApoE ε4 carrier status [carrier or non-carrier], geographical region), baseline value by assessment visit interaction, and treatment group by assessment visit interaction as fixed effects. An unstructured variance-covariance matrix was used for within-subject effects.

c, Adjusted mean ± standard error

The results for the key secondary efficacy endpoints are shown below: the change from baseline in ADAS-Cog14,[30] Alzheimer's Disease Cooperative Study-Activities of Daily Living Scale for Mild Cognitive Impairment (ADCS MCI-ADL),[40] and ADCOMS[27] at Month 18 (Table 42) and change from baseline in brain Aβ accumulation as measured by amyloid PET using the Centiloid scale (Table 43).

[39] ChE inhibitors and/or memantine

[40] The ADCS MCI-ADL is a scale consisting of 18 categories for the assessment of activities of daily living of patients with MCI. Changes in the patient's activities of daily living for the preceding month are assessed by the patient's caregiver, with the calculated score ranging from 0 to 53 points.

Table 42. Change from baseline in ADAS-Cog14, ADCS MCI-ADL, and ADCOMS (FAS+)

		Placebo	Lecanemab
ADAS-Cog14	Baseline[a]	N = 873 24.37 ± 7.56	N = 856 24.45 ± 7.08
	Month 18[a]	N = 740 28.55 ± 11.87	N = 705 28.00 ± 10.86
	Change from baseline (MMRM)[b, c]	N = 738 5.58 ± 0.31	N = 703 4.14 ± 0.31
	Adjusted mean difference between groups	—	−1.44
ADCS MCI-ADL	Baseline[a]	N = 822 40.9 ± 6.89	N = 808 41.2 ± 6.61
	Month 18[a]	N = 754 36.9 ± 10.03	N = 715 38.4 ± 9.13
	Change from baseline (MMRM)[b, c]	N = 707 −5.50 ± 0.31	N = 676 −3.48 ± 0.31
	Adjusted mean difference between groups	—	2.02
ADCOMS	Baseline[a]	N = 875 0.40 ± 0.15	N = 859 0.40 ± 0.15
	Month 18[a]	N = 749 0.58 ± 0.30	N = 708 0.54 ± 0.28
	Change from baseline (MMRM)[b, c]	N = 749 0.21 ± 0.01	N = 708 0.16 ± 0.01
	Adjusted mean difference between groups	—	−0.05

a, Mean ± standard deviation

b, Analyzed with an MMRM with baseline value as the covariate, with treatment group, assessment visit, stratification factors at randomization (clinical subgroup [MCI due to AD or mild AD-D], use/non-use of symptomatic AD medications, ApoE ε4 carrier status [carrier or non-carrier], geographical region), baseline value by assessment visit interaction, and treatment group by assessment visit interaction as fixed effects. An unstructured variance-covariance matrix was used for within-subject effects.

c, Adjusted mean ± standard error

Table 43. Change from baseline in brain Aβ accumulation as measured by amyloid PET using the Centiloid scale (PD analysis set)

	Placebo	Lecanemab
Baseline[a]	N = 351 75.03 ± 41.82	N = 360 77.92 ± 44.84
Month 18[a]	N = 206 78.16 ± 40.47	N = 211 22.99 ± 25.10
Change from baseline (MMRM)[b, c]	N = 205 3.64 ± 1.47	N = 210 −55.48 ± 1.46
Adjusted mean difference between groups	—	−59.12

a, Mean ± standard deviation

b, Analyzed with an MMRM with baseline value as the covariate, with treatment group, assessment visit, stratification factors at randomization (clinical subgroup [MCI due to AD or mild AD-D], use/non-use of symptomatic AD medications, ApoE ε4 carrier status [carrier or non-carrier], geographical region), baseline value by assessment visit interaction, and treatment group by assessment visit interaction as fixed effects. An unstructured variance-covariance matrix was used for within-subject effects.

c, Adjusted mean ± standard error

Table 44 shows the incidence of adverse events.

Table 44. Incidence of adverse events (Safety analysis set)

	Placebo (N = 897)	Lecanemab (N = 898)
All adverse events	81.9 (735)	88.9 (798)
Main events[a]		
Infusion related reaction	7.1 (64)	26.3 (236)
Amyloid related imaging abnormality-microhaemorrhages and haemosiderin deposits	7.7 (69)	14.0 (126)
Amyloid related imaging abnormality-oedema/effusion	1.7 (15)	12.6 (113)
Headache	8.1 (73)	11.1 (100)
Fall	9.6 (86)	10.4 (93)
Urinary tract infection	9.1 (82)	8.7 (78)
COVID-19	6.7 (60)	7.1 (64)
Back pain	5.8 (52)	6.7 (60)
Arthralgia	6.9 (62)	5.9 (53)
Superficial siderosis of central nervous system	2.5 (22)	5.6 (50)
Dizziness	5.1 (46)	5.5 (49)
Diarrhoea	6.5 (58)	5.3 (48)
Anxiety	4.2 (38)	5.0 (45)

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

There were 7 deaths in the placebo group (death, acute respiratory failure, myocardial infarction, metastases to bone, haemorrhage intracranial, COVID-19, and pancreatic carcinoma) and 6 deaths in the lecanemab group (death, cerebrovascular stroke, myocardial infarction, respiratory failure, metastases to meninges, COVID-19), and a causal relationship to the study drug was denied for all events. Other serious adverse events occurred in 94 subjects in the placebo group and 120 subjects in the lecanemab group. Serious adverse events occurring in ≥2 subjects in both groups were atrial fibrillation (3 subjects [placebo] and 6 subjects [lecanemab]), pneumonia (3 subjects [placebo] and 3 subjects [lecanemab]), subdural haematoma (3 subjects [placebo] and 3 subjects [lecanemab]), osteoarthritis (3 subjects [placebo] and 2 subjects [lecanemab]), acute respiratory failure (3 subjects [placebo] and 2 subjects [lecanemab]), inguinal hernia (2 subjects [placebo] and 3 subjects [lecanemab]), hip fracture (2 subjects [placebo] and 3 subjects [lecanemab]), transient ischaemic attack (2 subjects [placebo] and 3 subjects [lecanemab]), COVID-19 (2 [placebo] and 2 subjects [lecanemab]), and dehydration (2 [placebo] and 2 subjects [lecanemab]). A causal relationship to the study drug could not be ruled out for atrial fibrillation in 1 subject of the placebo group.

Adverse events led to treatment discontinuation of the study drug in 28 subjects in the placebo group and 64 subjects in the lecanemab group. Adverse events occurring in ≥2 subjects in either group were amyloid related imaging abnormality-microhaemorrhages and haemosiderin deposits (1 subject [placebo] and 15 subjects [lecanemab]), ARIA-E (0 subjects [placebo] and 14 subjects [lecanemab]), infusion related reaction (1 subject [placebo] and 12 subjects [lecanemab]), superficial siderosis of central nervous system (0 subjects [placebo] and 4 subjects [lecanemab]), depression (0 subjects [placebo] and 2 subjects [lecanemab]), myocardial infarction (2 subjects [placebo] and 1 subject [lecanemab]), and subdural haematoma (2 subjects [placebo] and 1 subject [lecanemab]). A causal relationship to the study drug could not be ruled out for all cases of amyloid related imaging abnormality-microhaemorrhages and haemosiderin deposits, ARIA-E, infusion related reaction, and superficial siderosis of central nervous system, and depression in 1 subject of the lecanemab group.

Japanese population

All 152 subjects who were enrolled in the Core study (64 subjects [placebo] and 88 subjects [lecanemab]) received the study drug, and were included in the safety analysis set. Of the safety analysis set, 151 subjects (64 subjects [placebo] and 87 subjects [lecanemab]) had evaluable data for the primary efficacy endpoint at baseline and ≥1 timepoint post-study dose, and were included in the FAS+, which was the primary efficacy analysis set. The PD analysis set comprised 38 subjects[41)] (17 subjects [placebo] and 21 subjects [lecanemab]) who had data that could be used to calculate ≥1 PD parameter. Seven Japanese subjects (3 subjects [placebo] and 4 subjects [lecanemab]) discontinued from the study, with common reasons for discontinuation being "adverse events" (3 subjects total; 2 subjects [placebo] and 1 subject [lecanemab]) and "withdrawal of consent" (2 subjects total; 1 subject [placebo] and 1 subject [lecanemab]). Concomitant symptomatic AD medications were used in 86 subjects (36 subjects [placebo] and 50 subjects [lecanemab]). Table 45 shows the ApoE ε4 carrier status.

Table 45. ApoE ε4 carrier status in each group (Japanese FAS+)

	Placebo	Lecanemab
ApoE ε4 carrier	71.9 (46)	71.3 (62)
Homozygous	14.1 (9)	16.1 (14)
Heterozygous	57.8 (37)	55.2 (48)
ApoE ε4 non-carrier	28.1 (18)	28.7 (25)

% (n)

Table 46 shows the change from baseline in CDR-SB at Month 18, the primary efficacy endpoint.

Table 46. Change from baseline in CDR-SB (Japanese FAS+)

	Placebo	Lecanemab
Baseline[a]	N = 64 2.95 ± 1.24	N = 87 2.79 ± 0.99
Month 18[a]	N = 60 3.89 ± 1.96	N = 84 3.76 ± 1.70
Change from baseline (MMRM)[b, c]	N = 60 1.16 ± 0.20	N = 84 1.08 ± 0.17
Adjusted mean difference between groups	—	−0.08

a, Mean ± standard deviation

b, Analyzed with an MMRM with baseline value as the covariate, with treatment group, assessment visit, stratification factors at randomization (clinical subgroup [MCI due to AD or mild AD-D], use/non-use of symptomatic AD medications, ApoE ε4 carrier status [carrier or non-carrier]), baseline value by assessment visit interaction, and treatment group by assessment visit interaction as fixed effects. An unstructured variance-covariance matrix was used for within-subject effects.

c, Adjusted mean ± standard error

The results for the key secondary efficacy endpoints are shown below: the change from baseline in ADAS-Cog14, ADCS MCI-ADL, and ADCOMS at Month 18 (Table 47) and change from baseline in brain Aβ accumulation as measured by amyloid PET using the Centiloid scale (Table 48).

41) The number of subjects who had amyloid PET data.

Table 47. Change from baseline in ADAS-Cog14, ADCS MCI-ADL, and ADCOMS (Japanese FAS+)

		Placebo	Lecanemab
ADAS-Cog14	Baseline[a]	N = 64 25.63 ± 6.06	N = 86 25.02 ± 4.78
	Month 18[a]	N = 60 29.55 ± 7.47	N = 83 28.52 ± 6.37
	Change from baseline (MMRM)[b, c]	N = 60 5.08 ± 0.78	N = 82 4.17 ± 0.68
	Adjusted mean difference between groups	—	−0.91
ADCS MCI-ADL	Baseline[a]	N = 49 39.3 ± 6.47	N = 70 39.7 ± 6.40
	Month 18[a]	N = 59 36.3 ± 7.57	N = 82 36.5 ± 7.91
	Change from baseline (MMRM)[b, c]	N = 45 −4.63 ± 0.89	N = 68 −3.70 ± 0.75
	Adjusted mean difference between groups	—	0.93
ADCOMS	Baseline[a]	N = 64 0.40 ± 0.13	N = 87 0.39 ± 0.12
	Month 18[a]	N = 60 0.55 ± 0.21	N = 83 0.52 ± 0.20
	Change from baseline (MMRM)[b, c]	N = 60 0.16 ± 0.02	N = 83 0.14 ± 0.02
	Adjusted mean difference between groups	—	−0.02

a, Mean ± standard deviation

b, Analyzed with an MMRM with baseline value as the covariate, with treatment group, assessment visit, stratification factors at randomization (clinical subgroup [MCI due to AD or mild AD-D], use/non-use of symptomatic AD medications, ApoE ε4 carrier status [carrier or non-carrier]), baseline value by assessment visit interaction, and treatment group by assessment visit interaction as fixed effects. An unstructured variance-covariance matrix was used for within-subject effects.

c, Adjusted mean ± standard error

Table 48. Change from baseline in brain Aβ accumulation as measured by amyloid PET using the Centiloid scale (Japanese PD analysis set)

	Placebo	Lecanemab
Baseline[a]	N = 17 68.59 ± 34.59	N = 21 82.35 ± 35.19
Month 18[a]	N = 13 71.01 ± 31.19	N = 19 12.85 ± 18.25
Change from baseline (MMRM)[b, c]	N = 13 −0.18 ± 5.55	N = 19 −68.41 ± 4.84
Adjusted mean difference between groups	—	−68.23

a, Mean ± standard deviation

b, Analyzed with an MMRM with baseline value as the covariate, with treatment group, assessment visit, stratification factors at randomization (clinical subgroup [MCI due to AD or mild AD-D], use/non-use of symptomatic AD medications, ApoE ε4 carrier status [carrier or non-carrier]), baseline value by assessment visit interaction, and treatment group by assessment visit interaction as fixed effects. An unstructured variance-covariance matrix was used for within-subject effects.

c, Adjusted mean ± standard error

Table 49 shows the incidence of adverse events.

Table 49. Incidence of adverse events (Japanese safety analysis set)

	Placebo (N = 64)	lecanemab (N = 88)
All adverse events	85.9 (55)	87.5 (77)
Main events[a]		
Amyloid related imaging abnormality-microhaemorrhages and haemosiderin deposits	14.1 (9)	12.5 (11)
Contusion	7.8 (5)	11.4 (10)
Infusion related reaction	1.6 (1)	10.2 (9)
Nasopharyngitis	7.8 (5)	9.1 (8)
Headache	7.8 (5)	5.7 (5)
Pain in extremity	3.1 (2)	5.7 (5)
Pyrexia	3.1 (2)	5.7 (5)
Constipation	9.4 (6)	5.7 (5)
Neck pain	0 (0)	5.7 (5)
Vaccination site pain	4.7 (3)	5.7 (5)
Malaise	1.6 (1)	5.7 (5)
Arthralgia	7.8 (5)	4.5 (4)
Rash	7.8 (5)	2.3 (2)
Eczema	6.3 (4)	2.3 (2)

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

There were no deaths. Other serious adverse events occurred in 9 subjects in the placebo group and 12 subjects in the lecanemab group, and there were no serious adverse events occurring in ≥2 subjects in either group.

Adverse events led to treatment discontinuation of the study drug in 2 subjects in the placebo group (injury and dementia with Lewy bodies) and 1 subject in the lecanemab group (bile duct stone and cholangitis), and a causal relationship to the study drug was denied for all events.

(b) Open-label extension phase

All subjects who entered OLE were to receive intravenous doses of lecanemab 10 mg/kg biweekly under open-label conditions at study centers. However, due to the COVID-19 pandemic situation, home treatment with intravenous lecanemab was allowed according to the regulations of the countries and regions.

Key eligibility criteria included patients who had completed Visit 42 (Week 79) of the Core study.

In subjects who developed ARIA-E or ARIA-H after their enrollment in the OLE phase, study drug treatment was to be continued or discontinued according to the criteria similar to those for Study 301 Core (Table 39). The use of concomitant symptomatic AD medications (ChE inhibitors and/or memantine) and prophylactic medications before study drug doses were equivalent to those implemented in Study 201 Core.

In the OLE phase, 964 subjects received the study drug and were included in the OLE treatment set. The safety analysis set comprised 1,391 subjects who received lecanemab in the Core or OLE, and the safety analysis period was defined as the period during which subjects received lecanemab in the Core or OLE. A total of 38 subjects discontinued from the study, with common reasons for discontinuation being “withdrawal of consent” (16 subjects), “adverse events” (11 subjects), and “subject’s choice” (7 subjects).

There were only a limited number of subjects with a lecanemab treatment duration of >6 months in OLE on the data cut-off date; therefore, no analyses were conducted using clinical assessment scales or biomarkers.

Table 50 shows the incidence of adverse events.

Table 50. Incidence of adverse events (Safety analysis set)

	Treated with lecanemab (N = 1391)
Overall incidence	80.6 (1121)
Main events[a]	
Infusion related reaction	24.0 (334)
Amyloid related imaging abnormality-microhaemorrhages and haemosiderin deposits	12.8 (178)
Amyloid related imaging abnormality-oedema/effusion	11.9 (166)
Headache	9.4 (131)
Fall	8.5 (118)
COVID-19	8.3 (115)
Urinary tract infection	7.4 (103)
Arthralgia	5.6 (78)
Back pain	5.5 (76)
Superficial siderosis of central nervous system	4.8 (67)
Dizziness	4.7 (65)
Anxiety	4.2 (59)
Diarrhoea	4.0 (56)
Hypertension	4.0 (55)

% (n)
a, Adverse events occurring in ≥4% of subjects

There were 9 deaths (6 in Core and 3 in OLE), and a causal relationship to the study drug was denied for all cases. Of the 3 subjects who died during OLE, 2 subjects (myocardial infarction and COVID-19 pneumonia) were receiving placebo in the Core study and 1 subject (cardiac failure acute) was receiving lecanemab in the Core study. Other serious adverse events occurred in 173 subjects. Serious adverse events occurring in ≥4 subjects were infusion related reaction (18 subjects), amyloid related imaging abnormality-oedema/effusion (11 subjects), atrial fibrillation (7 subjects), angina pectoris (6 subjects), pneumonia (6 subjects), syncope (6 subjects), urinary tract infection (5 subjects), acute myocardial infarction (4 subjects), amyloid related imaging abnormality-microhaemorrhages and haemosiderin deposits (4 subjects), COVID-19 pneumonia (4 subjects), cerebral haemorrhage (4 subjects), diverticulitis (4 subjects), fall (4 subjects), inguinal hernia (4 subjects), non-cardiac chest pain (4 subjects), and subdural haematoma (4 subjects). Serious adverse events in 40 subjects were determined to be related to the study drug, with common events being infusion related reaction (18 subjects), amyloid related imaging abnormality-oedema/effusion (11 subjects), and amyloid related imaging abnormality-microhaemorrhages and haemosiderin deposits (4 subjects).

Adverse events led to treatment discontinuation of the study drug in 82 subjects. Among these events, those that occurred in 57 subjects were determined to be related to the study drug, with common events being amyloid related imaging abnormality-oedema/effusion (18 subjects), infusion related reaction (18 subjects), and amyloid related imaging abnormality-microhaemorrhages and haemosiderin deposits (17 subjects).

7.R Outline of the review conducted by PMDA

7.R.1 Clinical positioning of lecanemab

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

Alzheimer's disease is a progressive, neurodegenerative disorder of unknown etiology and the most common form of dementia among older people. In patients with AD, decline in cognitive function progresses gradually. With the progression of AD, the ability to take initiative is reduced, basic motor abilities such as standing up and sitting down are lost, and the individual becomes bedridden in the final phase. The mean survival time after diagnosis of AD-D is typically 4 to 8 years (*Alzheimers Dement.* 2021;17:327-406). Alzheimer's disease medications approved in Japan include ChE inhibitors (donepezil, rivastigmine, galantamine) and *N*-methyl-D-aspartate (NMDA; memantine), all of which are symptomatic drugs and cannot inhibit the progression of the disease per se (*Cochrane Database Syst Rev.* 2006;1:CD005593, *Cochrane Database Syst Rev.* 2006;2:CD003154). Currently, no treatment drugs targeting the background pathology of AD have been approved in Japan, and there are great unmet needs for therapies that can slow the progression of the disease.

Amyloid β is a component of amyloid plaques in the brain, characteristic of AD. Both Aβ and phosphorylated tau are abnormal proteins that accumulate in patients with AD. The amyloid cascade hypothesis, the most prevalent hypothesis, postulates that accumulation of Aβ precedes the appearance of AD's clinical symptoms, and accumulated Aβ becomes neurotoxic, causing neurodegeneration (*Science.* 2002;297:353-6). On the basis of the hypothesis, criteria for the diagnosis of AD including the pre-dementia stage have been proposed. In addition, in recent years, early intervention with a disease-modifying therapy is expected to be an effective approach to delay disease progression of AD (*Front Aging Neurosci.* 2022;14:870517). Lecanemab is a recombinant humanized IgG1 monoclonal antibody targeting soluble AβPFs and is designed to bind selectively to the soluble AβPF, which is considered especially neurotoxic among other forms of Aβ (*J Alzheimers Dis.* 2015;43:575-88).

In the global phase III study in patients with early AD (Study 301), the results for CDR-SB, the primary endpoint, and multiple endpoints on other clinical symptoms suggested that lecanemab can slow the progression of AD compared with placebo, with similar effects irrespective of patient characteristics [see Section "7.R.3.2 Factors affecting the efficacy"]. In addition, the results indicated a clear effect of lecanemab, reducing the accumulation of Aβ in the brain [see Section "7.R.3.3 Biomarkers"]. The safety data showed that the risk of lecanemab including ARIA can be managed irrespective of *APOE4* genotype [see Section "7.R4 Safety"], and it is considered that lecanemab has a favorable risk-benefit balance.

On the basis of the above, lecanemab is expected to become a new treatment option for patients with early AD including ApoE ε4 carriers.

PMDA's view:

Since AD is the most common type of dementia, and there are currently no approved drugs that act on the pathology to slow the progression of disease, thus great unmet needs remain in the treatment of AD.

The amyloid cascade hypothesis, which postulates that the accumulation of Aβ in the brain triggers neurodegeneration, is one of the prevailing hypotheses when considering the pathology of AD. The amyloid cascade hypothesis has driven development of antibody drugs targeting Aβ; however, there have been no drugs that have demonstrated efficacy and none that have been approved in Japan. Lecanemab, a monoclonal antibody targeting soluble AβPFs, is considered to exert its treatment effect by a new mechanism of action, by which soluble AβPFs are removed by microglial phagocytosis. Study 201, which was conducted in patients with early AD, suggested a certain level of efficacy of lecanemab based on the clinical assessment scales such as CDR-SB up to Month 18, and the amyloid PET results indicated a reduction in accumulation of Aβ in the brain. In Study 301, a confirmatory study, indicated clinically meaningful efficacy. On the basis of the benefits demonstrated in Study 301, lecanemab has acceptable safety [see Sections "7.R.3 Efficacy" and "7.R.4 Safety"]. In view of the above results, it is considered clinically meaningful to make this new Aβ targeting therapy, the first in Japan, available in clinical settings as a new option for the treatment of patients with early AD. However, as discussed in Section 7.R.2 and subsequent sections, sufficient cautionary statements should be provided to healthcare professionals and patients to the effect that there are increased risks of adverse reactions such as ARIA and infusion reaction during treatment with lecanemab, and that periodic MRI and other forms of monitoring to ensure patient safety are necessary. In addition, further discussion is necessary on clarification of lecanemab's patient population, and on communication of the information required to periodically determine whether treatment should be continued.

7.R.2 Global phase III study (Study 301)

7.R.2.1 Appropriateness of Japan's participation in Study 301

The applicant's explanation about the appropriateness of Japan's participation in the global phase III study (Study 301):

Intrinsic ethnic factors are as follows: the PK parameters in steady state after 10 mg/kg biweekly administration of lecanemab in Japanese subjects were similar to those in non-Japanese subjects with no clear differences between the populations [see Section "6.R.1 Differences in PK between Japanese and non-Japanese populations"]. Among patients with AD-D who had confirmed amyloid pathology, the percentage of carriers of ApoE ε4, the strongest known genetic risk factor for AD (*J Neurol Neurosurg Psychiatry*. 2011;82:1149-56), was 67.7% in North America, 63.2% in Australia, 73.9% in Northern Europe, 65.2% in Central Europe, 47.5% in Southern Europe, and 54.9% in Asia, indicating that the ApoE ε4 status does not differ significantly between regions (*Alzheimers Dement.* 2018;14:913-24). In an Alzheimer's Disease Neuroimaging Initiative (ADNI) study in which patients in the US and Japan were followed for a prolonged period, from MCI to the onset of dementia, brain amyloid-positive patients with late MCI progressed to dementia at a rate of 24.7% (American) and 30.4% (Japanese) in 12 months, 31.2% (American) and 43.4% (Japanese) in 18 months, and 60.0% (American) and 63.5% (Japanese) in 36 months, indicating no clear difference in progression of AD between Japanese and non-Japanese populations.

Extrinsic ethnic factors are as follows: it is generally recommended to use the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), or the diagnostic criteria developed by the National Institute on Aging and Alzheimer's Association Workgroup (NIA-AA) for

the diagnosis of AD (*Clinical Practice Guidelines for Dementia* 2017 [in Japanese] Igaku-Shoin Ltd.; 2017:p210-3), and this situation does not differ significantly across countries participating in Study 301. In recent years, diagnostic criteria for AD incorporate the concept of the use of biomarkers such as accumulation of Aβ in the brain to identify AD pathology, and such criteria have been used in Japan and other countries, suggesting no clear differences in diagnosis of AD across regions. As for AD medications, there is no difference between Japan and other countries in the availability of symptomatic drugs, i.e., ChE inhibitors and memantine. Disease-modifying therapies, aducanumab and lecanemab, were approved in the US as of June 2023. However, no disease-modifying therapies had been approved in Japan or other countries at the start of the clinical study of lecanemab; therefore, the evaluation of the efficacy and safety of lecanemab in Study 301 is considered to be not influenced by AD medications in Japan and other countries.

In view of the above, Japan's participation in the global phase III study (Study 301) is appropriate.

PMDA's view:
On the basis of the applicant's explanation, there are no differences between Japan and other countries in intrinsic and extrinsic ethnic factors, which are crucial issues when conducting a global study in patients with early AD; therefore, Japan's participation in Study 301 is appropriate.

7.R.2.2 Efficacy endpoints

The applicant's explanation about the details of selecting the efficacy endpoints in Study 301 and the rationale for the selection:
Around 2012 when the global phase II study (Study 201) to evaluate efficacy in patients with early AD was designed, there were no standard, high-sensitivity clinical assessment scales to measure long-term progression of relatively mild clinical symptoms during early stages of AD or treatment effects had been established. Accordingly, using placebo group data from 4 studies in patients with MCI (ADNI MCI subgroup, Alzheimer's Disease Cooperative Study [ADCS], and 2 clinical studies of donepezil in patients with MCI), the applicant developed ADCOMS, which is a composite scale system sensitive to progression of clinical symptoms and treatment effect in patients with MCI. In Study 201 Core, ADCOMS was used as the primary endpoint and CDR-SB was selected as the key secondary endpoint. The ADCOMS consists of a total of 12 items from ADAS-Cog14 (4 of 14 items), MMSE (2 of 11 items), and CDR-SB (all 6 items), with score values ranging from 0 to 1.97. The results of ADCOMS and other clinical assessment scales from Study 201 Core suggested that ADCOMS, like CDR-SB, is a clinical assessment scale that can be used to assess adequately both cognitive function and activities of daily living of patients with early AD.

[redacted] According to the United States Food and Drug Administration (FDA) Guidance (*Alzheimer's Disease: Developing Drugs for the Treatment of Early Stage Disease Guidance for Industry*. Food And Drug Administration; 2013) and EMA Guidelines (*Draft guideline on the clinical investigation of medicines for the treatment of Alzheimer's disease and other dementias*.

European Medicines Agency; 2016), a composite scale validated to assess both cognitive function and activities of daily living can be used for a single primary efficacy endpoint in clinical studies in patients with early AD, and CDR-SB is mentioned as an example of an appropriate measure for an endpoint. The CDR-SB is a 'hybrid' scale consisting of 3 categories from the cognition domain (memory, orientation, and judgment and problem solving) and 3 categories from the function domain (community affairs, home and hobbies, and personal care) (*Int Psychogeriatr*. 1997;9 Suppl 1:173-6, *Journal of the American Geriatrics Society.* 2000;48:558-9), and is reported to be an appropriate, reliable, and responsive scale to assess long-term disease progression in patients with early AD (*Alzheimers Dement.* 2013;9:S45-55, *Neuropsychiatr Dis Treat.* 2014;10:929-52). After the release of the above-mentioned guidelines, CDR-SB has been used as the primary endpoint in confirmatory studies of drugs targeting Aβ.

In Study 301, therefore, CDR-SB was selected as the primary endpoint and ADCOMS as the key secondary endpoint. In addition, imaging and fluid biomarkers were also used in combination to evaluate the effect of lecanemab on the background pathology of AD. Taken together, the selection of efficacy endpoints in Study 301 is considered appropriate.

PMDA's view:

Because patients with early AD include patients with mild cognitive impairment or a mild degree of impairment in daily activities, there is a concern that endpoints used in the clinical studies of approved drugs for AD-D may not be able to detect the effect of lecanemab on clinical symptoms with sufficiently high sensitivity. Currently, no clinical assessment scales that can evaluate the efficacy (clinical significance of treatment intervention) of treatment drugs for early AD have been established. Taking into account the following aspects, it is concluded that the efficacy endpoints used in Study 301 can be considered a reasonable set of measures at present.

- The CDR-SB is a scale that can assess the change in clinical symptoms of patients with early AD, which is the patient population of Studies 201 and 301.
- In Study 301, the applicant plans to explain the efficacy of lecanemab by evaluating data in a comprehensive manner, in terms of not only the change from baseline in CDR-SB, the primary endpoint, but also changes from baseline by other clinical assessment scales and the amyloid PET Centiloid scale.

7.R.3 Efficacy

7.R.3.1 Significance of results from clinical studies

The applicant's explanation about the significance of the results of the lecanemab clinical studies:

The primary objective of Study 201 Core was to determine the most effective dosage regimen based on ADCOMS at Month 12. On the basis of data including the results of comparison between group difference in the change from baseline in ADCOMS, lecanemab 10 mg/kg biweekly was determined to be the most effective dosage regimen. The Bayesian analysis showed that the lecanemab 10 mg/kg biweekly regimen had a 64% probability of being superior to placebo by a clinically meaningful difference (defined as the difference calculated to slow progression of decline in ADCOMS by ≥25% compared with placebo after 1 year of lecanemab treatment), which did not meet the prespecified success criterion of >80%. However, the analysis

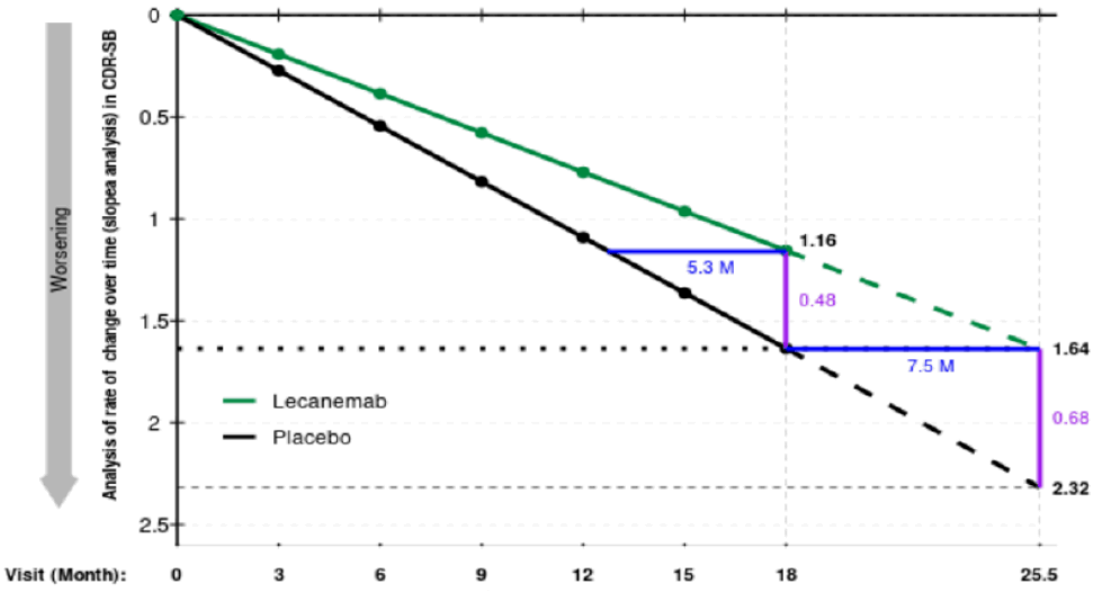
performed secondarily based on the frequentist approach (MMRM[42)]) indicated a dose-response relationship similar to the primary analysis, and the 10 mg/kg biweekly regimen most likely slows decline of ADCOMS, a result supporting the primary analysis results.

In the CDR used for the primary endpoint in Study 301 Core, each of 3 categories from the cognition domain and 3 categories from the function domain was rated on 5 degrees of impairment: 0 (none), 0.5 (questionable), 1 (mild), 2 (moderate), and 3 (severe), and the CDR-SB sums the scores of the 6 categories. The change in CDR-SB does not indicate detailed changes in patients; rather, it is a clinically meaningful change in the patient's daily living that can be felt by the patient, caregiver, or other persons.

There are no established methods to determine the minimal clinically meaningful difference on CDR-SB and other instruments to assess the effect of disease-modifying therapies for AD. While some studies in patients with early AD have reported a minimum clinically meaningful change in CDR-SB of 0.50 to 0.98 for MCI and 1.63 for mild AD-D (*J Prev Alzheimers Dis.* 2023;10:9-18, *Alzheimers Dement [NY].* 2023;9:e12388), a slowdown of reduction in CDR-SB by approximately 25% is considered clinically meaningful by other researchers (*J Prev Alzheimers Dis.* 2016;3:219-28). In Study 301 Core, the adjusted mean difference in change from baseline in CDR-SB at Month 18 between the groups (lecanemab minus placebo) was −0.451 (Table 41), indicating that its absolute value exceeds the absolute value of the prespecified clinically meaningful between-group difference, −0.373. In Study 201 Core, the adjusted mean difference in change from baseline in CDR-SB at Month 18 (MMRM) between lecanemab 10 mg/kg biweekly and placebo was −0.396, indicating that the result of Study 301 Core confirmed the efficacy indicated by the results of Study 201 Core.

At Month 18 in Study 301 Core, lecanemab slowed the decline in CDR-SB by 27.1% ([between group difference in change from baseline in CDR-SB] / [change from baseline in CDR-SB in placebo] × 100) compared with placebo, suggesting a clinically meaningful slowing effect on the progression of symptoms. Furthermore, the change over time in CDR-SB was analyzed with a linear mixed model using the mean slope values based on data from Study 301 Core up to Month 18. The results showed that lecanemab slowed by approximately 5.3 months the decline in CDR-SB over the 18 month-period compared with placebo. It is estimated that lecanemab would not reach the 18-month placebo level of worsening in CDR-SB until 7.5 months later (Figure 1).

[42)] An MMRM with baseline value as the covariate, with treatment group, assessment visit, stratification factors at randomization (disease stage [MCI due to AD or mild AD-D], ApoE ε4 carrier status [carrier or non-carrier], use/non-use of symptomatic AD medications at baseline [AChE inhibitor and/or memantine]), geographical region, and treatment group by assessment visit interaction as fixed effects.



The data up to Month 18 were used in the analysis, and the same slope was assumed after Month 18 (projection beyond Month 18 is indicated by dotted lines)

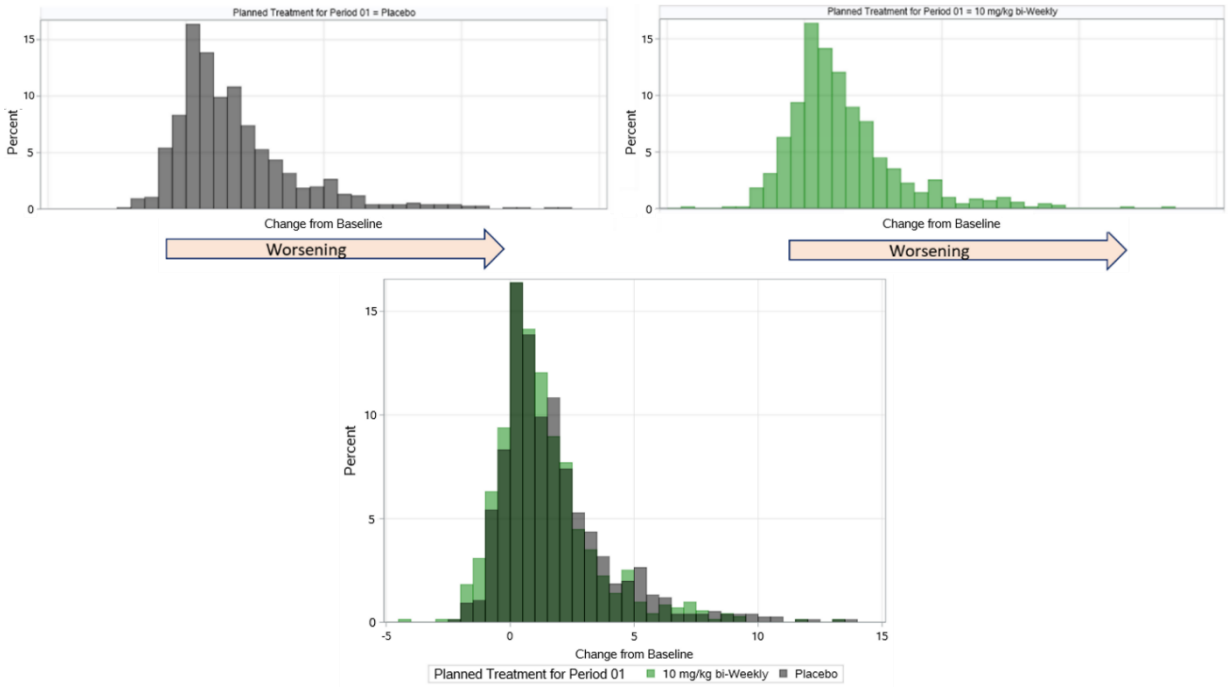
Figure 1. Linear mixed model analysis of change from baseline in CDR-SB over time in Study 301 Core (FAS+)

The results for key secondary efficacy endpoints in Study 301 Core (Table 42), the change from baseline in ADAS-Cog14 (cognitive function) and ADCS MCI-ADL (activities of daily living), showed that lecanemab tended to slow worsening of the scores for both endpoints. The hazard ratio of disease progression[43)] to the next stage on the CDR score at Month 18 in the lecanemab group compared with placebo was 0.69 [two-sided 95% CI: 0.572, 0.833].

PMDA asked the applicant to show the distribution of change from baseline in CDR-SB at Month 18 for each subject in Study 301 Core by treatment group and then explain the difference between lecanemab and placebo.

The applicant's explanation:
Figure 2 shows the distribution of change from baseline in CDR-SB at Month 18 for each subject in Study 301 Core by treatment group. The proportion of subjects whose CDR-SB indicated improvement or a lesser degree of worsening in the overall population tended to be higher in the lecanemab group than in the placebo group.

[43)] Defined as time from randomization to worsening of the CDR scores (i.e., time to the visit of the first worsening with an increase from baseline by ≥0.5 in the CDR score on 2 consecutive visits).



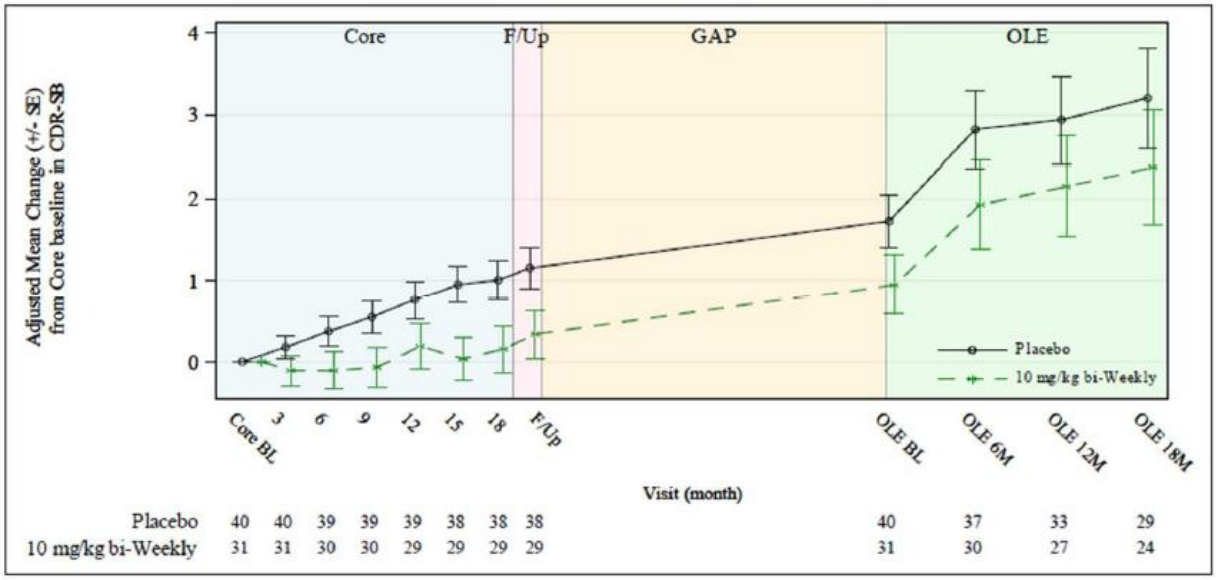
The placebo group (upper left graph); lecanemab group (upper right graph); overlay of the both groups (lower graph)

Figure 2. Distribution of change from baseline in CDR-SB at Month 18 for each subject in Study 301 Core by treatment group (FAS+)

The applicant's explanation about the long-term efficacy of lecanemab:

Figure 3 shows the change from Core baseline in CDR-SB over time in subjects who had been assigned to placebo or lecanemab 10 mg/kg biweekly in Study 201 Core, and received lecanemab 10 mg/kg biweekly in OLE. The results of the gap period (off-treatment period, ranging 9–59 months depending on subjects, with a mean of 24 months[44)]) suggested that the effect of lecanemab is maintained after the completion of treatment. The CDR-SB scores continued to increase after the start of OLE up to Month 6 both in subjects treated with placebo and in those treated with lecanemab 10 mg/kg biweekly in the Core study, and thereafter, the rate of increase became more gradual. The difference in change from Core baseline in CDR-SB between those treated with placebo and those treated with lecanemab 10 mg/kg biweekly at the start of OLE tended to be maintained with treatment in OLE. These results suggested that initiation of treatment with lecanemab in the early stages of AD and continuation of treatment would enhance long-term clinical effects, and that lecanemab has a disease-modifying effect, namely, to slow the progression of disease in patients with early AD.

[44)] The OLE phase started after the completion of the Core study data analysis, which resulted in various duration of the gap period depending on subjects.



All subjects were off-treatment with the study drug during the gap period (ranging 9–59 months depending on subjects); all subjects received lecanemab 10 mg/kg biweekly in OLE.

Figure 3. Change from Core baseline in CDR-SB over time in Study 201 (OLE-FAS, excluding subjects with conditions that had progressed beyond early AD)

In view of the above, the results from the clinical studies of lecanemab have shown that lecanemab demonstrates meaningful effects on slowing clinical decline of AD.

PMDA's view:

Although the results of Study 201 Core did not meet the prespecified success criterion, the results of assessments including CDR-SB (Table 24) suggested the efficacy of lecanemab 10 mg/kg biweekly.

Study 301 Core, a confirmatory study, indicated a significant effect of lecanemab on slowing decline in CDR-SB compared with placebo, with the absolute value of the difference between the groups exceeding the value estimated in advance (Table 41). The change from baseline in CDR-SB in the lecanemab group differed from that of placebo by 0.451, which is less than the minimum unit of change of score, 0.5; however, it is concluded that the efficacy of lecanemab is clinically meaningful based on the primary analysis results as well as the following factors:

- The results demonstrated slowing of CDR-SB decline with a difference of 27.1% with lecanemab compared with placebo. Since symptoms of AD progress gradually over a long period, slowing of the progress by approximately 20% at an early stage is considered to be meaningful to a certain extent.
- The hazard ratio of disease progression to the next stage on the CDR score in the lecanemab group compared with placebo was 0.69 [two-sided 95% CI: 0.572, 0.833], suggesting that lecanemab may slow the progression from MCI due to AD to AD-D and from mild to moderate or severe AD-D.
- The results for ADAS-Cog14 and ADCS MCI-ADL, secondary endpoints, support the efficacy of lecanemab in cognitive function and activities of daily living in patients with early AD.

In Study 201 OLE, the difference in the treatment effect between lecanemab 10 mg/kg biweekly and placebo in Study 201 Core was maintained after the gap period during which subjects were not treated with lecanemab. On the basis of this and other factors, PMDA considers as follows regarding the applicant's argument that lecanemab is expected to have a disease-modifying effect. Study 201 Core and Study 301 Core showed that lecanemab slowed the progression of clinical symptoms such as cognitive impairment, and the results for lecanemab were more favorable compared with placebo for biomarkers considered to be associated with AD pathology. However, as discussed later in Section "7.R.3.3 Biomarkers," changes in clinical symptoms were not clearly correlated with the changes in biomarkers; and no statistical testing was designed in either study to evaluate the disease-modifying effect of lecanemab; therefore, current data are not sufficient to conclude that the disease-modifying effects of lecanemab 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 the efficacy

The applicant gave an explanation on the factors that can affect the efficacy of lecanemab. Note that only the results of subgroup analysis in Study 301 Core were used because patient characteristics were not equally distributed due to the modification of the study design in Study 201 Core [see Section "7.2 Global phase II study"].

Table 51 shows the results of subgroup analysis on change from baseline in CDR-SB at Month 18 in Study 301 Core by the following factors at baseline: use or non-use of symptomatic AD medications (ChE inhibitors and/or memantine), disease stage, ApoE ε4 carrier status, geographical region, and amyloid PET Centiloid scale. With the exception of ApoE ε4 carrier status, the results of subgroup analysis based on patient characteristics showed no significant difference between each subgroup and the overall population. In addition to the patient characteristic factors shown above, similar subgroup analyses were performed for several factors including age and sex, and the results indicated no significant difference between each subgroup and the overall population.

Table 51. Change from baseline in CDR-SB at Month 18 in Study 301 Core by the use or non-use of symptomatic AD medications, disease stage, ApoE ε4 carrier status, geographical region, and amyloid PET Centiloid scale at baseline (FAS+)

		Change (MMRM)[a]		Adjusted mean difference between groups
		Placebo	Lecanemab	
Overall population		N = 757 1.663 ± 0.080	N = 714 1.213 ± 0.082	−0.451
Symptomatic AD medication	Not used	N = 344 1.379 ± 0.112	N = 348 0.993 ± 0.110	−0.386
	Used	N = 413 1.931 ± 0.115	N = 366 1.450 ± 0.121	−0.481
Disease stage	MCI due to AD	N = 487 1.270 ± 0.085	N = 460 0.916 ± 0.087	−0.354
	Mild AD-D	N = 270 2.280 ± 0.163	N = 254 1.659 ± 0.165	−0.621
ApoE ε4 carrier status[b]	Carrier	N = 526 1.607 ± 0.095	N = 501 1.273 ± 0.096	−0.334
	Homozygous	N = 117 1.281 ± 0.223	N = 113 1.557 ± 0.224	0.276
	Heterozygous	N = 409 1.692 ± 0.104	N = 388 1.189 ± 0.105	−0.503
	Non-carrier	N = 231 1.840 ± 0.147	N = 213 1.093 ± 0.151	−0.747
Geographical region	North America	N = 427 1.508 ± 0.102	N = 405 0.991 ± 0.103	−0.517
	Europe[c]	N = 190 2.278 ± 0.178	N = 174 1.950 ± 0.183	−0.328
	Asia Pacific[d]	N = 140 1.425 ± 0.156	N = 135 1.076 ± 0.158	−0.349
Baseline amyloid PET Centiloid scale	<30	N = 68 1.003 ± 0.254	N = 72 0.561 ± 0.241	−0.442
	≥30 and <80	N = 202 1.652 ± 0.144	N = 180 0.887 ± 0.150	−0.765
	≥80	N = 341 1.928 ± 0.124	N = 315 1.529 ± 0.130	−0.399

a, Adjusted mean ± standard error
b, *APOE4* genotype (homozygous or heterozygous) was not considered as a factor at randomization.
c, Including Australia
d, Japan, South Korea, and Singapore

In the subgroup analysis based on ApoE ε4 carrier status, the results for the non-carrier subgroup and ApoE ε4 heterozygous carrier subgroup did not differ significantly from those for the overall population. Conversely, the results for the homozygous subgroup did not show a trend towards slowing decline compared with placebo, which is not consistent with the results for the overall population. This inconsistency can be attributed to the more gradual decline in CDR-SB in the homozygous placebo group compared with that in the placebo group of the overall population. The trend of CDR-SB observed in the homozygous placebo group is an unexpected result, and does not agree with the finding that the number of ApoE ε4 alleles does not affect the rate of progression in cognitive decline in patients with early AD (*Alzheimers Dement.* 2020;6:e12007). The smaller size of the homozygous subgroup (15.5%) compared with other groups may have resulted in a larger variation of data. The adjusted mean difference in change from baseline in ADAS-Cog14 and in ADCS MCI-ADL at Month 18 in Study 301 Core between lecanemab and placebo in the homozygous subgroup was −0.528 for ADAS-Cog14 and 1.032 for ADCS MCI-ADL, and did not differ clearly from that in the overall population, −1.442 and 2.016, respectively. In the homozygous subgroup, a reduction in the accumulated Aβ levels in the

brain (amyloid PET Centiloid scale) and improvements in plasma and CSF biomarkers associated with amyloid, tau, and neurodegeneration were observed in the lecanemab group compared with placebo, results consistent with those of the overall population. Therefore, lecanemab is expected to show efficacy irrespective of the *APOE4* genotype.

In view of the discussions above, no factors that may have a clear impact on the efficacy of lecanemab have been identified from the currently available data.

PMDA's view:
On the basis of the results of subgroup analyses of factors that may have effects on the efficacy of lecanemab, no factors tended to have a significant effect on the efficacy of lecanemab except for ApoE ε4 homozygous carrier. The limited number of eligible ApoE ε4 homozygous carriers precludes any definitive interpretation. In light of this and results of subgroup analyses of other endpoints as well as findings on the relationship between ApoE ε4 status and progression of AD, there is no likely mechanism that leads to waning of the efficacy of lecanemab, and therefore, it is considered that lecanemab can be expected to show efficacy. Therefore, provided patients meet the Study 301 Core eligibility criteria, lecanemab is expected to show efficacy regardless of the use/non use of symptomatic AD medications, disease stage (MCI due to AD or mild AD-D), ApoE ε4 carrier status, and amyloid PET Centiloid scale at baseline. The appropriateness of the decision above will be finalized taking into account the comments from the Expert Discussion. The efficacy by geographic region will be discussed in Section "7.R.3.4 Efficacy in Japanese patients."

7.R.3.3 Biomarkers

The applicant's explanation about the relationship between the change in biomarkers and clinical assessment scales in Study 201 Core and Study 301 Core:

(a) Amyloid PET

Table 52 shows the change from baseline in amyloid PET Centiloid scale over time in Study 301 Core. The accumulated Aβ levels in the brain reduced in the lecanemab group compared with placebo at all timepoints after Month 3. The mean Centiloid scale for the lecanemab group was 77.9 at baseline and decreased to 23.0 at Month 18, which is lower than the threshold for amyloid positivity of 30 Centiloids.[45)]

[45)] The threshold for amyloid positivity was defined as amyloid PET SUVr of 1.17 (*Arch Neurol* 2011;68:1404-11), corresponding to a Centiloid threshold of 30. The threshold of 30 Centiloid agrees well with cut-off values for visual read (e.g., *Alzheimers Res Ther.* 2020;12:22, *Alzheimers Res Ther.* 2021;13:67), pathological judgment (*Eur J Nucl Med Mol Imaging.* 2017;44:2053-9), or determining brain amyloid accumulation based on the p-tau/Aβ42 ratio and t-tau/Aβ42 ratio in CSF (*Alzheimers Res Ther.* 2019;11:27).

Table 52. Change from baseline in amyloid PET Centiloid scale over time in Study 301 Core (PD analysis set [Amyloid PET])

	Placebo	Lecanemab
Baseline[a]	N = 351 75.026 ± 41.8240	N = 360 77.918 ± 44.8389
Change from baseline at Month 6 (MMRM)[b]	N = 286 2.587 ± 1.246	N = 275 −33.627 ± 1.254
Adjusted mean difference between groups [two-sided 95% CI]	—	−36.214 [−39.012, −33.417]
Change from baseline at Month 12 (MMRM)[b]	N = 259 2.988 ± 1.394	N = 276 −49.026 ± 1.380
Adjusted mean difference between groups [two-sided 95% CI]	—	−52.014 [−55.280, −48.748]
Change from baseline at Month 18 (MMRM)[b]	N = 205 3.637 ± 1.470	N = 210 −55.481 ± 1.457
Adjusted mean difference between groups [two-sided 95% CI]	—	−59.118 [−62.640, −55.596]

a, Mean ± standard deviation; b, Adjusted mean ± standard error

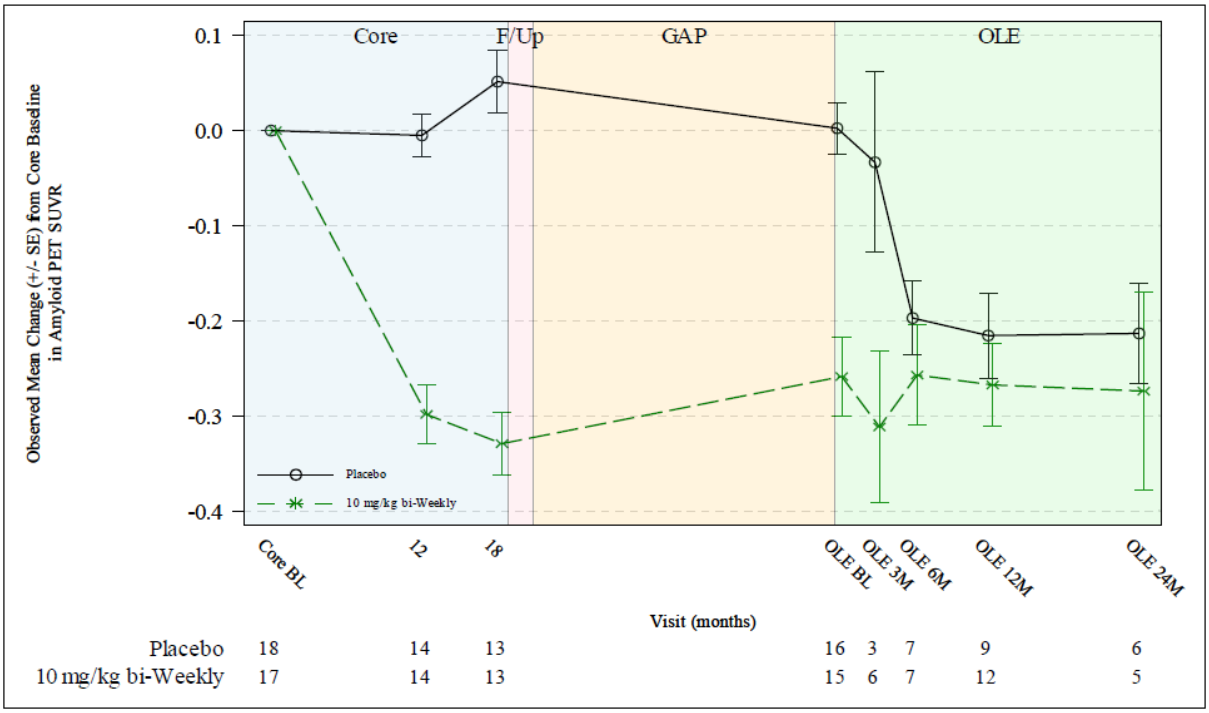
Table 53 shows the change over time in the proportion of subjects with amyloid PET status converted from amyloid positive to amyloid negative as measured by Centiloid scale in Study 301 Core (<30 Centiloids[45)]). The proportion of subjects with amyloid status converted from positive to negative was higher in the lecanemab group than in the placebo group at all timepoints from Month 3 (0.8% placebo and 5.5% lecanemab) up to Month 18.

Table 53. Change over time in the proportion of subjects who converted from amyloid positive to amyloid negative as measured by Centiloid scale in Study 301 Core (PD analysis set [Amyloid PET])

	Placebo	Lecanemab
Baseline	N = 294	N = 291
Month 6	0.4 (1/243)	22.8 (52/228)
Month 12	0.9 (2/219)	43.6 (98/225)
Month 18	0.6 (1/172)	60.4 (102/169)

% (n/N)

Figure 4 shows the change from Core baseline over time in amyloid PET SUVr in Study 201. During the treatment period of the Core study, amyloid PET SUVr increased slightly in the placebo group but decreased significantly in the lecanemab 10 mg/kg biweekly group. After the interruption of treatment with lecanemab (follow-up period and gap period [off-treatment period, ranging 9–59 months depending on subjects, with a mean of 24 months]), the amyloid PET SUVr increased in the lecanemab 10 mg/kg biweekly group, which was considered the consequence of natural history of Aβ accumulation in the brain, which can be predicted in patients with AD. During OLE, a decrease in amyloid PET SUVr by lecanemab 10 mg/kg biweekly treatment was observed regardless of treatment in the Core study, and the higher the OLE baseline, the greater the reduction. The mean amyloid PET SUVr at Month 12 and Month 24 in OLE were below the threshold for amyloid positivity (1.17 Centiloids[45)]) in subjects receiving placebo and those receiving lecanemab 10 mg/kg biweekly in the Core study.



All subjects were off-treatment with the study drug during the gap period (ranging 9–59 months depending on subjects); all subjects received lecanemab 10 mg/kg biweekly in OLE.

Figure 4. Change from Core baseline over time in amyloid PET SUVr in Study 201 (OLE enrollment group)

(b) Tau PET

The composite regions (temporal lobe, medial temporal lobe, and meta-temporal lobe) are known to accumulate tau in the early stages of AD. Table 54 shows the change from baseline over time in tau PET SUVr (tracer, ^{18}F-MK-6240) in Study 301 Core. In all 3 regions, change from baseline in tau PET SUVr in the lecanemab group decreased compared with placebo.

Table 54. Change from baseline in tau PET in Study 301 Core
(PD analysis set [tau PET])

	Temporal lobe		Medial temporal lobe		Meta-temporal lobe	
	Placebo	Lecanemab	Placebo	Lecanemab	Placebo	Lecanemab
Change from baseline at Month 13 (MMRM)[a]	N = 115 0.119 ± 0.068	N = 128 0.045 ± 0.071	N = 115 0.063 ± 0.055	N = 128 −0.003 ± 0.057	N = 115 0.118 ± 0.071	N = 128 0.042 ± 0.073
Adjusted mean difference between groups	—	−0.074	—	−0.066	—	−0.076
Change from baseline at Month 18 (MMRM)[a]	N = 107 0.144 ± 0.069	N = 103 0.079 ± 0.071	N = 107 0.086 ± 0.055	N = 103 0.018 ± 0.057	N = 107 0.145 ± 0.071	N = 103 0.073 ± 0.074
Adjusted mean difference between groups	—	−0.065	—	−0.068	—	−0.071

a, Adjusted mean ± standard error

(c) CSF biomarkers[46)]

Table 55 shows the change from baseline over time in CSF Aβ (1-42), CSF phosphorylated tau (p-tau) 181, CSF total tau (t-tau), and CSF neurogranin in Study 301 Core. There were greater reductions in CSF p-tau181,

[46)] CSF biomarkers were not studied in Japanese subjects.

CSF t-tau, and CSF neurogranin with lecanemab than with placebo, and a greater increase in CSF Aβ (1-42) with lecanemab than with placebo.

Table 55. Change from baseline over time in CSF Aβ (1-42), CSF p-tau181, CSF t-tau, and CSF neurogranin in Study 301 Core (PD analysis set [CSF])

		Placebo	Lecanemab
Aβ (1-42)	Baseline[a]	N = 137 514.416 ± 232.9245	N = 142 546.979 ± 253.3085
	Change from baseline at Month 12 (MMRM)[b]	N = 125 −1.026 ± 27.273	N = 125 247.819 ± 27.852
	Adjusted mean difference between groups [two-sided 95% CI]	—	248.845 [196.053, 301.637]
	Change from baseline at Month 18 (MMRM)[b]	N = 97 −2.542 ± 26.740	N = 101 287.283 ± 27.148
	Adjusted mean difference between groups [two-sided 95% CI]	—	289.824 [238.514, 341.134]
p-tau181	Baseline[a]	N = 139 92.081 ± 48.0908	N = 142 84.922 ± 46.0150
	Change from baseline at Month 12 (MMRM)[b]	N = 126 8.939 ± 2.716	N = 123 −13.196 ± 2.798
	Adjusted mean difference between groups [two-sided 95% CI]	—	−22.135 [−27.158, −17.112]
	Change from baseline at Month 18 (MMRM)[b]	N = 98 12.356 ± 2.964	N = 101 −16.108 ± 3.013
	Adjusted mean difference between groups [two-sided 95% CI]	—	−28.464 [−34.477, −22.451]
t-tau	Baseline[a]	N = 139 615.216 ± 340.4945	N = 142 584.993 ± 316.9654
	Change from baseline at Month 12 (MMRM)[b]	N = 126 77.909 ± 21.325	N = 125 −32.628 ± 21.916
	Adjusted mean difference between groups [two-sided 95% CI]	—	−110.536 [−149.749, −71.323]
	Change from baseline at Month 18 (MMRM)[b]	N = 98 94.496 ± 22.510	N = 101 −30.433 ± 22.949
	Adjusted mean difference between groups [two-sided 95% CI]	—	−124.929 [−169.062, −80.796]
Neurogranin	Baseline[a]	N = 134 519.060 ± 281.3503	N = 139 500.094 ± 277.6637
	Change from baseline at Month 12 (MMRM)[b]	N = 127 1.744 ± 14.577	N = 130 −61.522 ± 15.107
	Adjusted mean difference between groups [two-sided 95% CI]	—	−63.266 [−89.414, −37.118]
	Change from baseline at Month 18 (MMRM)[b]	N = 97 18.293 ± 17.908	N = 104 −71.367 ± 18.118
	Adjusted mean difference between groups [two-sided 95% CI]	—	−89.660 [−128.258, −51.061]

pg/mL
a, Mean ± standard deviation; b, Adjusted mean ± standard error

(d) Plasma biomarkers

Table 56 shows the change from baseline over time in plasma Aβ42/40 ratio, plasma p-tau181, and plasma neurofilament light chain (NfL) in Study 301 Core. The increase in the plasma Aβ42/40 ratio was greater with lecanemab than with placebo, and the reductions in plasma p-tau181 and plasma NfL were also greater with lecanemab.

Table 56. Change from baseline over time in plasma Aβ42/40 ratio, plasma p-tau181, and plasma NfL in Study 301 Core (PD analysis set [Plasma])

		Placebo	Lecanemab
Aβ42/40 ratio	Baseline[a]	N = 811 0.088 ± 0.0091	N = 814 0.088 ± 0.0087
	Change from baseline at Month 6 (MMRM)[b]	N = 757 0.000 ± 0.000	N = 743 0.003 ± 0.000
	Adjusted mean difference between groups [two-sided 95% CI]	—	0.004 [0.003, 0.004]
	Change from baseline at Month 12 (MMRM)[b]	N = 704 0.000 ± 0.000	N = 703 0.006 ± 0.000
	Adjusted mean difference between groups [two-sided 95% CI]	—	0.007 [0.006, 0.007]
	Change from baseline at Month 18 (MMRM)[b]	N = 668 0.001 ± 0.000	N = 648 0.008 ± 0.000
	Adjusted mean difference between groups [two-sided 95% CI]	—	0.007 [0.006, 0.008]
p-tau181[c]	Baseline[a]	N = 763 3.740 ± 1.7197	N = 766 3.696 ± 1.9581
	Change from baseline at Month 6 (MMRM)[b]	N = 696 0.230 ± 0.046	N = 679 −0.217 ± 0.046
	Adjusted mean difference between groups [two-sided 95% CI]	—	−0.448 [−0.562, −0.333]
	Change from baseline at Month 12 (MMRM)[b]	N = 640 0.278 ± 0.048	N = 636 −0.466 ± 0.048
	Adjusted mean difference between groups [two-sided 95% CI]	—	−0.744 [−0.864, −0.624]
	Change from baseline at Month 18 (MMRM)[b]	N = 609 0.201 ± 0.050	N = 590 −0.575 ± 0.050
	Adjusted mean difference between groups [two-sided 95% CI]	—	−0.776 [−0.904, −0.648]
NfL[c]	Baseline[a]	N = 746 22.205 ± 11.5584	N = 728 21.899 ± 11.2514
	Change from baseline at Month 6 (MMRM)[b]	N = 655 2.332 ± 0.514	N = 611 2.335 ± 0.529
	Adjusted mean difference between groups [two-sided 95% CI]	—	0.003 [−1.373, 1.380]
	Change from baseline at Month 12 (MMRM)[b]	N = 595 2.594 ± 0.434	N = 582 2.014 ± 0.437
	Adjusted mean difference between groups [two-sided 95% CI]	—	−0.580 [−1.702, 0.542]
	Change from baseline at Month 18 (MMRM)[b]	N = 574 2.944 ± 0.458	N = 529 1.838 ± 0.472
	Adjusted mean difference between groups [two-sided 95% CI]	—	−1.106 [−2.318, 0.105]

a, Mean ± standard deviation; b, Adjusted mean ± standard error; c, pg/mL

(e) Relationship between biomarkers and clinical assessment scales

The subject-level correlation between the change from baseline in the amyloid PET Centiloid scale and change from baseline in CDR-SB at Month 18 in Study 301 Core, and the scatter plots for the changes are shown in Table 57 and Figure 5, respectively. In Study 201 Core, the reduction in Aβ accumulation in the brain as measured by amyloid PET SUVr was suggested to correlate with a slowing in the decline of clinical symptoms as measured by CDR-SB at the population level (Pearson correlation coefficient = 0.805). In both Study 201 Core and Study 301 Core, however, at the subject level, the correlation was not strong enough to predict the change from baseline in CDR-SB or other efficacy endpoints based on the change from baseline in amyloid PET SUVr or Centiloid scale in subjects with reduced amyloid accumulation after lecanemab treatment. This is probably due to factors including varying clinical courses of symptoms in each subject resulting from

difference in disease stage or use/non-use of symptomatic AD medications, and possibility that the clinical efficacy of lecanemab may not become apparent until slightly after the reduction in amyloid accumulation. Note that amyloid PET is used only for qualitative determination of positivity and negativity in clinical practice (*Guidelines for Proper Use of Amyloid PET Imaging Agent.* Second Edition. [in Japanese] Japanese Society of Nuclear Medicine; 2017), and its use for the prediction of clinical efficacy at the individual level has not been established.

Table 57. Subject-level correlation between the change from baseline in amyloid PET Centiloid scale and change from baseline in CDR-SB at Month 18 in Study 301 Core (Of the FAS+, those included in the PD analysis set [Amyloid PET])

	Placebo	Lecanemab
Correlation between change from baseline in Aβ PET at Month 6 and change from baseline in CDR-SB at Month 18	−0.056	−0.016
Correlation between change from baseline in Aβ PET at Month 12 and change from baseline in CDR-SB at Month 18	−0.117	−0.140
Correlation between change from baseline in Aβ PET at Month 18 and change from baseline in CDR-SB at Month 18	−0.053	−0.165

Pearson Correlation coefficient

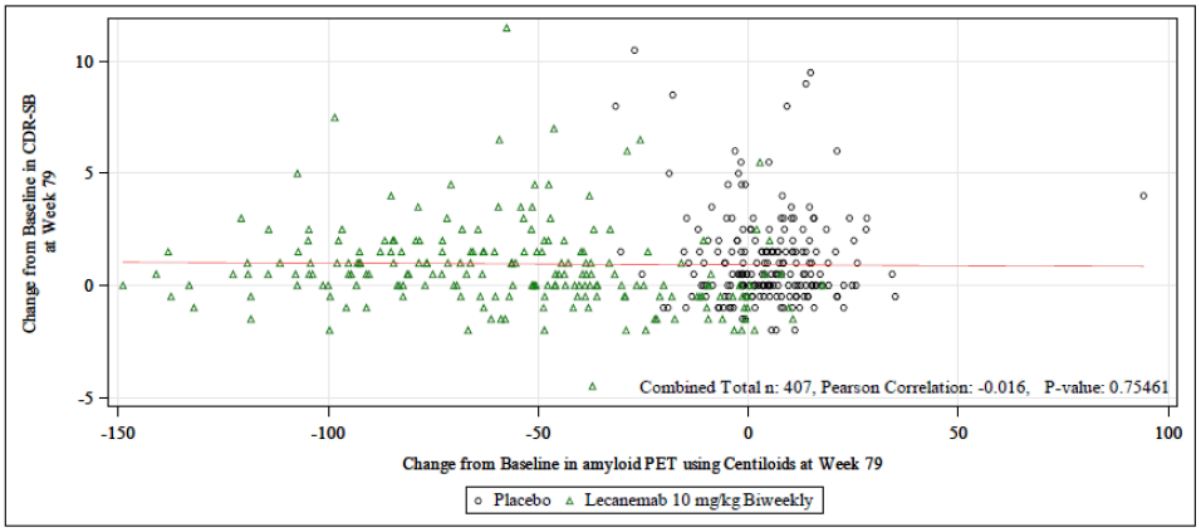


Figure 5. Scatter plots for the change from baseline in amyloid PET Centiloid scale and for the change from baseline in CDR-SB in Study 301 Core (Of the FAS+, those included in the PD analysis set [Amyloid PET])

PMDA asked the applicant to show the change from baseline in CDR-SB in the patient group which showed conversion from amyloid positive to negative and that which did not show conversion from amyloid positive to negative after treatment with lecanemab, and then explain whether lecanemab can be expected to show its efficacy in patients who have not become amyloid negative.

The applicant's explanation:

Figure 6 shows the plots for the change from baseline over time in CDR-SB in patients who were determined to be amyloid positive based on the visual read in amyloid PET at baseline in Study 301 Core. The decline in CDR-SB was more gradual in the group receiving lecanemab compared with placebo irrespective of the timing

of conversion to amyloid negative as determined by visual read. The results of the group that became amyloid negative and the results of the group that did not become amyloid negative after treatment with lecanemab were analyzed. While the decline in CDR-SB was more gradual in the group that became amyloid negative compared with the group that did not become amyloid negative, the results suggested the decline in CDR-SB was slower in the group that did not become amyloid negative compared with the group receiving placebo. Therefore, lecanemab is expected to show its efficacy also in patients who do not become amyloid negative.

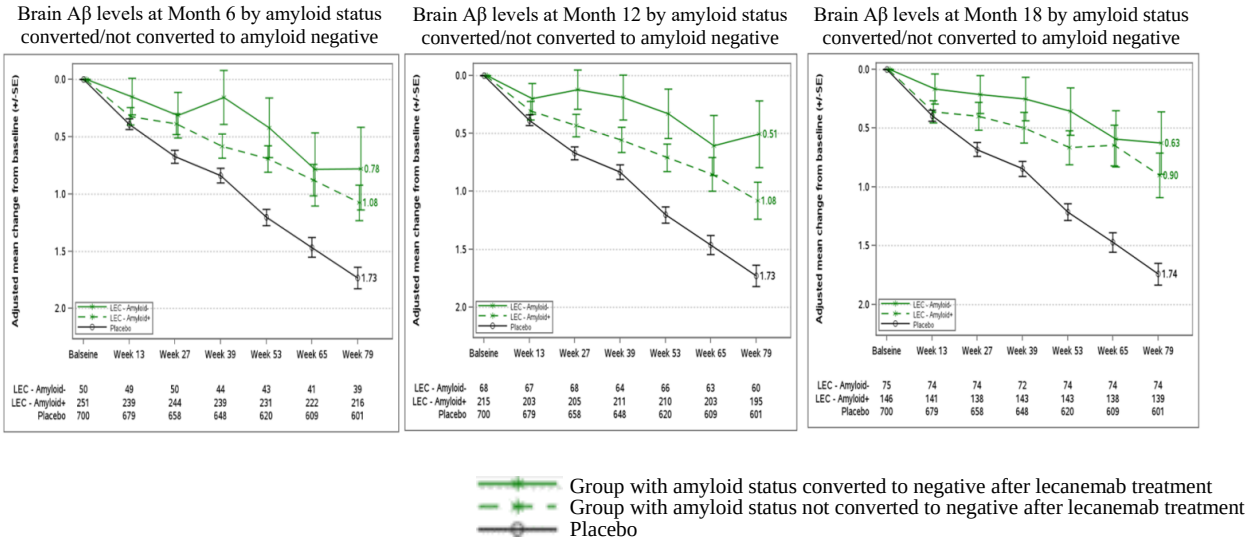


Figure 6. Change from baseline over time in CDR-SB in patients who were determined to be amyloid positive based on the visual read in amyloid PET at baseline in Study 301 Core

On the basis of the investigations in (a) through (e) above, given the changes in biomarkers and clinical assessment scales after lecanemab 10 mg/kg biweekly treatment as described below, lecanemab is considered to directly remove amyloid pathology and slow progression of AD including tau pathology downstream of amyloid pathology and neurodegenerative process, thereby exerting a disease-modifying effect.

- A time-dependent reduction of Aβ accumulation in the brain
- Increase in plasma Aβ42/40 ratio and CSF Aβ (1-42), which are biomarkers associated with brain amyloid pathology and are negatively correlated with amyloid accumulation in the brain (*Neurology*. 2019;93:e1647-59)
- Reduction of tau pathology-associated biomarkers: tau accumulation in the brain as measured by tau PET SUVr, plasma p-tau, and CSF p-tau
- Reduction of neurodegenerative process-associated biomarker: CSF t-tau

PMDA's view:

Changes in biomarkers in Study 201 Core and Study 301 Core suggest the following. A reduction in Aβ accumulation in the brain as measured by amyloid PET, increase in CSF Aβ (1-42), and reduction in p-tau and t-tau, which are predicted from the mechanism of action of lecanemab, can be interpreted as the effects of lecanemab on biomarkers associated with AD pathology observed in humans. However, given that there were

no clear correlations between the reduction in brain Aβ levels as measured by amyloid PET and change in clinical symptoms, it is difficult to determine the treatment effect of lecanemab based on the change from baseline in any of the biomarkers evaluated in Study 301 Core [see Section "7.R.3.1 Significance of results from clinical studies" for the PMDA's conclusion on disease-modifying effects]. Therefore, PMDA concluded that a decision as to whether lecanemab has efficacy or treatment should be continued should be made based on the clinical course of symptoms [see Section "7.R.6.2 Decision on continuation or discontinuation of treatment"].

7.R.3.4 Efficacy in Japanese patients

The applicant's explanation about the efficacy in the Japanese population:

(a) Clinical assessment scale

A sample size of 120 Japanese subjects (60 subjects/group) was selected to evaluate[47)] whether the efficacy results in the Japanese population were consistent with those of the overall population in Study 301 Core, and 151 subjects were enrolled (Japanese FAS+).

The difference in adjusted mean change from baseline in CDR-SB at Month 18, the primary endpoint of Study 301, in lecanemab compared with placebo was −0.079 in the Japanese population (Japanese FAS+; the same applies hereinafter), with a 6.8% slowing of decline compared with placebo, indicating a trend towards slowing of decline consistent with the results for the overall population (FAS+; the same applies hereinafter) (Table 41). The difference in adjusted mean change from baseline in ADAS-Cog14, ADCOMS, and ADCS MCI-ADL at Month 18 (key secondary endpoints) in lecanemab compared with placebo was −0.907, −0.022, and 0.929, respectively, corresponding to 17.9%, 13.4%, and 20.1% slowing of decline compared with placebo, respectively, each indicating a trend towards slowing of decline consistent with the results for the overall population (Table 42). In each clinical assessment scale, the percentage of slowing of decline compared with placebo tended to be lower in the Japanese population than in the overall population, which is assumed to be attributable to a lesser degree of worsening in all of the clinical assessment scales in Japanese subjects receiving placebo compared with the overall population receiving placebo. The demographic and baseline characteristics of the Japanese population were consistent except for the mean body weight being lower than that of the overall population (55.76 kg and 71.11 kg, respectively). Body weight is a factor identified as a significant covariate for CL and V_c in the PPK analysis [see Section "6.R.1 Differences in PK between Japanese and non-Japanese populations"]. The $C_{ss,ave}$ at steady state in subjects treated with lecanemab 10 mg/kg biweekly in Study 301 Core was estimated by a PPK analysis model. The $C_{ss,ave}$ tended to be slightly lower in the Japanese population compared with that of the group excluding Japanese and South Korean subjects; however, the difference was within the range of inter-individual variability, and difference in exposure is unlikely to have affected the efficacy of lecanemab. The disease-associated characteristics at baseline of the Japanese population were consistent with the overall population. While the baseline proportion of subjects with a CDR score of 0.5

47) Assuming that the change from baseline in CDR-SB at Month 18 (primary endpoint) in Japanese patients would be consistent with the overall population, the sample size was selected taking into account of the following factors: first, between group difference for the primary endpoint should be significant in the overall population; in addition, the sample size should be the conditional probability of ≥80% to satisfy the between group difference for the primary endpoint (lecanemab minus placebo) in Japanese patients <0 (a trend towards slowing of worsening is indicated based on point estimates).

(94.0%) and the proportion of subjects diagnosed as having MCI due to AD in clinical diagnosis of early AD (70.9%) were slightly higher than those in the overall population (80.7% and 61.8%, respectively), given that lecanemab tended to slow worsening of CDR-SB score regardless of disease stage (MCI due to AD or mild AD-D) in the overall population (Table 51), it is unlikely that the difference in the baseline CDR score and disease stage have affected the efficacy of lecanemab.

On the basis of the above, it is unlikely that differences in patient characteristics between the Japanese population and the overall population have affected the efficacy of lecanemab, and the variability resulting from the limited number of Japanese subjects was thought to have affected the interpretation of results.

(b) Biomarkers

The difference in adjusted mean change from baseline in amyloid PET Centiloid scale at Month 18, a key secondary endpoint in Study 301 Core, in lecanemab compared with placebo was −68.233 in the Japanese population. The brain levels of accumulated Aβ decreased compared with placebo at all timepoints after Month 3, a result consistent with that for the overall population (Table 43). The mean Centiloid scale in the lecanemab group decreased to 12.853 at Month 18, lower than the threshold for amyloid positivity of 30 Centiloids.[45)]

In addition to the investigation results in (a) and (b), the ADNI studies conducted in the US and Japan indicated no difference in the rate of progression of clinical symptoms of MCI due to AD between Japanese and Caucasian patients (*Alzheimers Dement.* 2018;14:1077-87). In view of the above, no data have suggested any obvious causes that would lead to the efficacy of lecanemab being any different in the Japanese population; therefore, as demonstrated in the overall population, lecanemab is also expected to show efficacy in Japanese patients.

PMDA's view:

The difference in change from baseline in CDR-SB in Study 301 Core in the Japanese population compared with placebo was <0, indicating the efficacy of lecanemab; however, the difference in the absolute value between lecanemab and placebo was less than that for the overall population. According to the applicant's explanation, this was due to the fact that the degree of worsening in the Japanese placebo group tended to be less than that in the placebo group of the overall population. However, the applicant's explanation has not clarified the reason that led to the different behavior of the Japanese placebo group from that of the placebo group of the overall population. PMDA comprehensively reviewed the efficacy-related issues including the following, and concluded that lecanemab is expected to show efficacy in Japanese patients consistent with the results for efficacy in the overall population.

- As explained by the applicant, the subgroup analyses in Japanese subjects were performed in a limited number of subjects, and the assessment of CDR-SB, which varies greatly between patients, is subject to a certain level of uncertainty.
- Currently available information such as observational studies of AD (e.g., ADNI) conducted in Japan and other countries have indicated no trend towards difference in the rate of progression of early AD in Japanese patients compared with the rate in other ethnic groups.

- As shown below, the differences[48] between the groups in the clinical assessment scales and biomarkers for the secondary endpoints show a trend suggesting that lecanemab has efficacy compared with placebo in the Japanese population, consistent with the results in the overall population.
  - ADAS Cog14: −1.44 (overall) and −0.91 (Japanese)
  - ADCS MCI-ADL: 2.02 (overall) and 0.93 (Japanese)
  - ADCOMS: −0.05 (overall) and −0.02 (Japanese)
  - Amyloid PET Centiloid scale: −59.12 (overall) and −68.23 (Japanese)

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

7.R.4 Safety

On the basis of the incidence of adverse events in the clinical studies, post-marketing information in other countries, and results of discussions in the following sections, as well as the efficacy of lecanemab demonstrated in Section "7.R.3 Efficacy," PMDA concluded that lecanemab has clinically acceptable safety in patients with early AD. Note that evaluation in this section is based on the combined data set consisting of data from Studies 201 OLE, 301 Core, and 301 OLE, in which the proposed dosage regimen was basically used, because (1) several dosage levels different from the proposed dosage regimen were used in Study 201 Core; and (2) patient characteristics were not equally distributed due to the modification of the study design [see Section 7.2 "Global phase II study"].

7.R.4.1 Amyloid-related imaging abnormalities

(a) ARIA-E

The applicant's explanation about ARIA-E:

Table 58 shows the incidence of ARIA-E in Studies 301 Core, 201 OLE, and 301 OLE. The majority of ARIA-E events in the lecanemab group occurred within the first 6 months of treatment irrespective of *APOE4* genotype (homozygous or heterozygous), and most of the ARIA-E resolved on imaging within 4 months of onset irrespective of severity. In all studies, no events of ARIA-E resulted in death.

[48] The adjusted mean difference (lecanemab minus placebo) in change from baseline at Month 18

Table 58. Incidence of ARIA-E in Study 201 OLE and Study 301 (Safety analysis set)

	301 Core		201 OLE	301 OLE
	Placebo (N = 897)	Lecanemab (N = 898)	Lecanemab (N = 180)	Lecanemab (N = 1391)
Incidence of ARIA-E	1.7 (15)	12.6 (113)	7.8 (14)	11.9 (166)
Details of subjects developing ARIA-E[a]				
Severity on MRI				
Mild	60.0 (9)	32.7 (37)	21.4 (3)	33.7 (56)
Moderate	40.0 (6)	58.4 (66)	50.0 (7)	56.6 (94)
Severe	0 (0)	8.0 (9)	28.6 (4)	9.0 (15)
Missing	0 (0)	0.9 (1)	0 (0)	0.6 (1)
Presence of symptoms				
Asymptomatic	100 (15)	77.9 (88)	78.6 (11)	78.9 (131)
Symptomatic, mild	0 (0)	8.8 (10)	7.1 (1)	8.4 (14)
Symptomatic, moderate	0 (0)	10.6 (12)	14.3 (2)	9.0 (15)
Symptomatic, severe	0 (0)	2.7 (3)	0 (0)	3.6 (6)
Main symptoms associated with ARIA-E				
Headache	0 (0)	10.6 (12)	14.3 (2)	11.4 (19)
Confusional state	0 (0)	3.5 (4)	0 (0)	3.0 (5)
Dizziness	0 (0)	2.7 (3)	7.1 (1)	1.8 (3)
Nausea	0 (0)	2.7 (3)	0 (0)	1.8 (3)
Aphasia	0 (0)	0.9 (1)	0 (0)	1.2 (2)
Generalised tonic-clonic seizure	0 (0)	0.9 (1)	0 (0)	1.2 (2)
Recurrence	6.7 (1)	24.8 (28)	28.6 (4)	18.7 (31)
Serious adverse events	0 (0)	6.2 (7)	7.1 (1)	6.6 (11)
Adverse events leading to study drug treatment discontinuation	0 (0)	12.4 (14)	0 (0)	10.8 (18)
Outcome				
Resolved	80.0 (12)	99.1 (112)	92.9 (13)	96.4 (160)
Not resolved	20.0 (3)	0.9 (1)	7.1 (1)	3.6 (6)
Time to onset[b] of the first ARIA-E in each treatment period				
≤13 weeks	33.3 (5)	70.8 (80)	71.4 (10)	72.9 (121)
>13 weeks and ≤27 weeks	33.3 (5)	21.2 (24)	21.4 (3)	18.7 (31)
>27 weeks and ≤39 weeks	6.7 (1)	0 (0)	0 (0)	0 (0)
>39 weeks and ≤53 weeks	13.3 (2)	7.1 (8)	7.1 (1)	4.8 (8)
>53 weeks and ≤65 weeks	0 (0)	0 (0)	0 (0)	0 (0)
>65 weeks and ≤79 weeks	13.3 (2)	0.9 (1)	0 (0)	0.6 (1)
>79 weeks and ≤105 weeks			0 (0)	3.0 (5)
>105 weeks and ≤133 weeks			0 (0)	0 (0)
>133 weeks and ≤157 weeks			0 (0)	0 (0)
>157 weeks			0 (0)	0 (0)
Time to resolution of first ARIA-E in each treatment period				
≤30 days after onset	20.0 (3)	8.8 (10)	0 (0)	10.2 (17)
>30 days and ≤40 days after onset	20.0 (3)	8.0 (9)	7.1 (1)	9.0 (15)
>40 days and ≤50 days after onset	0 (0)	0.9 (1)	7.1 (1)	1.2 (2)
>50 days and ≤60 days after onset	0 (0)	15.0 (17)	7.1 (1)	13.3 (22)
>60 days and ≤70 days after onset	6.7 (1)	8.8 (10)	0 (0)	6.6 (11)
>70 days and ≤80 days after onset	0 (0)	3.5 (4)	14.3 (2)	2.4 (4)
>80 days and ≤90 days after onset	13.3 (2)	7.1 (8)	14.3 (2)	11.4 (19)
>90 days and ≤120 days after onset	6.7 (1)	28.3 (32)	14.3 (2)	24.7 (41)
>120 days and ≤150 days after onset	6.7 (1)	8.8 (10)	0 (0)	10.2 (17)
>150 days after onset	6.7 (1)	10.6 (12)	28.6 (4)	7.8 (13)

% (n)

a, Percentage values below this were calculated using the number of subjects with ARIA-E events as the denominator.

b, Number of days after the start of study drug treatment (Study 301 Core); after the start of OLE (Study 201 OLE); after the start of study drug treatment (Core lecanemab group in Study 301 OLE); after the start of OLE (Core placebo group in Study 301 OLE)

Table 59 shows the list of subjects who developed serious ARIA-E in Studies 301 Core (lecanemab group), 201 OLE, and 301 OLE. Serious ARIA-E occurred in 7 subjects in the lecanemab group of Study 301 Core, with a time to onset of 8 to 535 days after the start of treatment with lecanemab. The majority of serious ARIA-E resolved by treatment interruption or discontinuation. Clinical outcome in 1 subject was reported to be

unresolved, and the course of the event was unknown after discontinuation from the study. Serious ARIA-E occurred in 4 subjects in Study 301 OLE (3 subjects were treated with placebo and 1 subject treated with lecanemab in Study 301 Core). Among these, the subject treated with lecanemab in Study 301 Core developed serious ARIA-E on Day 41 of OLE (Day 589 from the start of Study 301 Core).

Table 59. List of subjects who developed serious ARIA-E in Studies 301 Core (lecanemab group), 201 OLE, and 301 OLE (Safety analysis set)

	Treatment in Core study	MCI /AD	Age (years)	Sex	Race	ApoE ε4 status	Onset (days)	Clinical severity	ARIA-H	Lecanemab treatment	Clinical outcome
301 Core	Lecanemab	AD	8[redacted]	[redacted]	[redacted]	Non-carrier	39	Moderate	Yes	Discontinued	Resolved
		MCI	6[redacted]	[redacted]	[redacted]	Carrier	44	Moderate	Yes	Discontinued	Resolved
		MCI	7[redacted]	[redacted]	[redacted]	Carrier	535	Mild	Yes	Discontinued	Not resolved
		MCI	8[redacted]	[redacted]	[redacted]	Carrier	72	Severe	Yes	Discontinued	Resolved
		AD	7[redacted]	[redacted]	[redacted]	Non-carrier	8	Moderate	No	Discontinued	Resolved
		MCI	6[redacted]	[redacted]	[redacted]	Carrier	35	Severe	Yes	Discontinued	Resolved
		MCI	6[redacted]	[redacted]	[redacted]	Carrier	156	Severe	Yes	Discontinued	Resolved
201 OLE	Lecanemab 5 mg/kg monthly	AD	8[redacted]	[redacted]	[redacted]	Carrier	181[a]	Mild	Yes	Continued	Resolved
301 OLE	Placebo	MCI	8[redacted]	[redacted]	[redacted]	Carrier	32[a]	Severe	Yes	Discontinued	Resolving
		AD	6[redacted]	[redacted]	[redacted]	Carrier	57[a]	Mild	No	Interrupted	Resolved
		AD	8[redacted]	[redacted]	[redacted]	Carrier	27[a]	Severe	Yes	Discontinued	Resolving
	Lecanemab	MCI	7[redacted]	[redacted]	[redacted]	Carrier	41[a]	Moderate	Yes	Discontinued	Resolved

a, Number of days after the start of OLE

The tables below show the incidence of ARIA-E by ApoE ε4 status (carrier or non-carrier) and *APOE4* genotype (heterozygous or homozygous) in Study 301 Core (Table 60) and Studies 201 OLE and 301 OLE (Table 61). The incidence of ARIA-E was higher in ApoE ε4 carriers than in non-carriers, and among ApoE ε4 carriers, the incidence was higher in homozygous ApoE ε4 carriers than in heterozygous ApoE ε4 carriers.

Table 60. Incidence of ARIA-E in Study 301 Core by ApoE ε4 carrier status and by *APOE4* genotype (Safety analysis set)

	Placebo			Lecanemab		
	ApoE ε4 carrier		ApoE ε4 non-carrier (N = 286)	ApoE ε4 carrier		ApoE ε4 non-carrier (N = 278)
	Homozygous (N = 133)	Heterozygous (N = 478)		Homozygous (N = 141)	Heterozygous (N = 479)	
Incidence of ARIA-E	3.8 (5)	1.9 (9)	0.3 (1)	32.6 (46)	10.9 (52)	5.4 (15)
Details of subjects developing ARIA-E[a]						
Severity on MRI						
Mild	40.0 (2)	77.8 (7)	0 (0)	13.0 (6)	48.1 (25)	40.0 (6)
Moderate	60.0 (3)	22.2 (2)	100 (1)	71.7 (33)	46.2 (24)	60.0 (9)
Severe	0 (0)	0 (0)	0 (0)	15.2 (7)	3.8 (2)	0 (0)
Missing	0 (0)	0 (0)	0 (0)	0 (0)	1.9 (1)	0 (0)
Presence of symptoms						
Asymptomatic	100 (5)	100 (9)	100 (1)	71.7 (33)	84.6 (44)	73.3 (11)
Symptomatic, mild	0 (0)	0 (0)	0 (0)	10.9 (5)	7.7 (4)	6.7 (1)
Symptomatic, moderate	0 (0)	0 (0)	0 (0)	15.2 (7)	3.8 (2)	20.0 (3)
Symptomatic, severe	0 (0)	0 (0)	0 (0)	2.2 (1)	3.8 (2)	0 (0)

% (n)

a, Percentage values below this were calculated using the number of subjects with ARIA-E events as the denominator.

Table 61. Incidence of ARIA-E in Studies 201 OLE and 301 OLE by ApoE ε4 carrier status and *APOE4* genotype (Safety analysis set)

	201 OLE			301 OLE		
	Lecanemab			Lecanemab		
	ApoE ε4 carrier		ApoE ε4 non-carrier (N = 55)	ApoE ε4 carrier		ApoE ε4 non-carrier (N = 470)
	Homozygous (N = 28)	Heterozygous (N = 97)		Homozygous (N = 206)	Heterozygous (N = 715)	
Incidence of ARIA-E	14.3 (4)	9.3 (9)	1.8 (1)	30.6 (63)	10.5 (75)	6.0 (28)
Details of subjects developing ARIA-E[a]						
Severity on MRI						
Mild	50.0 (2)	11.1 (1)	0 (0)	20.6 (13)	40.0 (30)	46.4 (13)
Moderate	0 (0)	66.7 (6)	100 (1)	68.3 (43)	48.0 (36)	53.6 (15)
Severe	50.0 (2)	22.2 (2)	0 (0)	11.1 (7)	10.7 (8)	0 (0)
Missing	0 (0)	0 (0)	0 (0)	0 (0)	1.3 (1)	0 (0)
Presence of symptoms						
Asymptomatic	75.0 (3)	88.9 (8)	0 (0)	73.0 (46)	82.7 (62)	82.1 (23)
Symptomatic, mild	0 (0)	0 (0)	100 (1)	11.1 (7)	6.7 (5)	7.1 (2)
Symptomatic, moderate	25.0 (1)	11.1 (1)	0 (0)	14.3 (9)	4.0 (3)	10.7 (3)
Symptomatic, severe	0 (0)	0 (0)	0 (0)	1.6 (1)	6.7 (5)	0 (0)

% (n)

a, Percentage values below this were calculated using the number of subjects with ARIA-E events as the denominator.

(b) ARIA-H

The applicant's explanation about ARIA-H:

Table 62 shows the incidence of ARIA-H in Studies 301 Core, 201 OLE, and 301 OLE. The majority of ARIA-H events were asymptomatic and many of the events were determined to be mild or moderate in severity on imaging. Among the subcategories of ARIA-H, cerebral microhemorrhage occurred most frequently while cerebral hemorrhage occurred least frequently, and ARIA-H (cerebral hemorrhage) resulted in death in 1 subject in the placebo group in Study 301 Core.

Table 62. Incidence of ARIA-H in Study 201 OLE and Study 301 (Safety analysis set)

	301 Core		201 OLE	301 OLE
	Placebo (N = 897)	Lecanemab (N = 898)	Lecanemab (N = 180)	Lecanemab (N = 1391)
Incidence of ARIA-H	9.0 (81)	17.3 (155)	16.1 (29)	15.3 (213)
Details of reported ARIA-H				
Incidence by subcategory				
Cerebral microhemorrhage	7.6 (68)	14.0 (126)	13.3 (24)	12.8 (178)
Superficial siderosis	2.3 (21)	5.6 (50)	4.4 (8)	4.8 (67)
Cerebral hemorrhage	0.1 (1)	0.6 (5)	0.6 (1)	0.4 (6)
Details of subjects developing ARIA-H[a]				
Severity on MRI				
Mild	90.1 (73)	62.6 (97)	65.5 (19)	65.3 (139)
Moderate	6.2 (5)	16.8 (26)	20.7 (6)	16.4 (35)
Severe	3.7 (3)	20.6 (32)	10.3 (3)	18.3 (39)
Missing	0 (0)	0 (0)	3.4 (1)	0 (0)
Presence of symptoms				
Asymptomatic	97.5 (79)	91.6 (142)	96.6 (28)	92.0 (196)
Symptomatic, mild	1.2 (1)	5.2 (8)	0 (0)	4.2 (9)
Symptomatic, moderate	1.2 (1)	2.6 (4)	3.4 (1)	2.8 (6)
Symptomatic, severe	0 (0)	0.6 (1)	0 (0)	0.9 (2)
Main symptoms associated with ARIA-H				
Headache	0 (0)	2.6 (4)	3.4 (1)	2.8 (6)
Dizziness	1.2 (1)	1.9 (3)	0 (0)	1.4 (3)
Confusional state	0 (0)	1.3 (2)	0 (0)	1.4 (3)
Serious adverse events	1.2 (1)	3.2 (5)	6.9 (2)	3.8 (8)
Adverse events leading to study drug treatment discontinuation	2.5 (2)	11.6 (18)	0 (0)	9.9 (21)

% (n)
a, Percentage values below this were calculated using the number of subjects with ARIA-H events as the denominator.

Tables below show the incidence of ARIA-H by ApoE ε4 status (carrier or non-carrier) and *APOE4* genotype (heterozygous or homozygous) in Study 301 Core (Tables 63) and Studies 201 OLE and 301 OLE (Table 64). The incidence of ARIA-H was higher in ApoE ε4 carriers than in non-carriers, and among ApoE ε4 carriers, the incidence was higher in homozygous ApoE ε4 carriers than in heterozygous ApoE ε4 carriers.

Table 63. Incidence of ARIA-H by ApoE ε4 status and *APOE4* genotype in Study 301 Core (Safety analysis set)

	Placebo			Lecanemab		
	ApoE ε4 carrier		ApoE ε4 non-carrier (N = 286)	ApoE ε4 carrier		ApoE ε4 non-carrier (N = 278)
	Homozygous (N = 133)	Heterozygous (N = 478)		Homozygous (N = 141)	Heterozygous (N = 479)	
Incidence of ARIA-H	21.1 (28)	8.6 (41)	4.2 (12)	39.0 (55)	14.0 (67)	11.9 (33)
Details of subjects developing ARIA-H[a]						
Severity on MRI						
Mild	85.7 (24)	95.1 (39)	83.3 (10)	40.0 (22)	71.6 (48)	81.8 (27)
Moderate	14.3 (4)	2.4 (1)	0 (0)	25.5 (14)	13.4 (9)	9.1 (3)
Severe	0 (0)	2.4 (1)	16.7 (2)	34.5 (19)	14.9 (10)	9.1 (3)
Missing	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Presence of symptoms						
Asymptomatic	96.4 (27)	97.6 (40)	100 (12)	90.9 (50)	92.5 (62)	90.9 (30)
Symptomatic, mild	3.6 (1)	0 (0)	0 (0)	5.5 (3)	6.0 (4)	3.0 (1)
Symptomatic, moderate	0 (0)	2.4 (1)	0 (0)	3.6 (2)	0 (0)	6.1 (2)
Symptomatic, severe	0 (0)	0 (0)	0 (0)	0 (0)	1.5 (1)	0 (0)

% (n)
a, Percentage values below this were calculated using the number of subjects with ARIA-H events as the denominator.

Table 64. Incidence of ARIA-H by ApoE ε4 status and *APOE4* genotype in Studies 201 OLE and 301 OLE (Safety analysis set)

	201 OLE			301 OLE		
	Lecanemab			Lecanemab		
	ApoE ε4 carrier		ApoE ε4 non-carrier (N = 55)	ApoE ε4 carrier		ApoE ε4 non-carrier (N = 470)
	Homozygous (N = 28)	Heterozygous (N = 97)		Homozygous (N = 206)	Heterozygous (N = 715)	
Incidence of ARIA-H	46.4 (13)	12.4 (12)	7.3 (4)	34.0 (70)	13.4 (96)	10.0 (47)
Details of subjects developing ARIA-H[a]						
Severity on MRI[b]						
Mild	—	—	—	42.9 (30)	71.9 (69)	85.1 (40)
Moderate	—	—	—	21.4 (15)	16.7 (16)	8.5 (4)
Severe	—	—	—	35.7 (25)	11.5 (11)	6.4 (3)
Missing	—	—	—	0 (0)	0 (0)	0 (0)
Presence of symptoms						
Asymptomatic	100 (13)	100 (12)	75.0 (3)	90.0 (63)	92.7 (89)	93.6 (44)
Symptomatic, mild	0 (0)	0 (0)	0 (0)	5.7 (4)	4.2 (4)	2.1 (1)
Symptomatic, moderate	0 (0)	0 (0)	25.0 (1)	4.3 (3)	1.0 (1)	4.3 (2)
Symptomatic, severe	0 (0)	0 (0)	0 (0)	0 (0)	2.1 (2)	0 (0)

% (n)
a, Percentage values below this were calculated using the number of subjects with ARIA-H events as the denominator.
b, Results by ApoE ε4 status were not calculated for Study 201 OLE.

Table 65 shows the incidence of ARIA-H with or without concurrent ARIA-E in Studies 301 Core, 201 OLE, and 301 OLE. The incidence of ARIA-H without concurrent ARIA-E in the lecanemab group was similar to that in the placebo group, while the incidence of ARIA-H with concurrent ARIA-E in the lecanemab group was higher in the lecanemab group than in the placebo group.

Table 65. Incidence of ARIA-H with or without concurrent ARIA-E in Study 201 OLE and Study 301 (Safety analysis set)

	301 Core		201 OLE	301 OLE
	Placebo (N = 897)	Lecanemab (N = 898)	Lecanemab (N = 180)	Lecanemab (N = 1391)
Incidence of ARIA-H with concurrent ARIA-E	1.0 (9)	8.2 (74)	4.4 (8)	7.5 (104)
Incidence by subcategory				
Cerebral microhemorrhage	0.3 (3)	7.1 (64)	3.3 (6)	6.5 (90)
Superficial siderosis	0.9 (8)	2.8 (25)	1.7 (3)	2.7 (37)
Cerebral hemorrhage	0 (0)	0.1 (1)	0 (0)	0.1 (2)
Incidence of ARIA-H without concurrent ARIA-E	7.8 (70)	8.9 (80)	11.7 (21)	7.5 (105)
Incidence by subcategory				
Cerebral microhemorrhage	7.0 (63)	6.7 (60)	10.0 (18)	6.3 (88)
Superficial siderosis	1.4 (13)	2.6 (23)	2.8 (5)	2.2 (30)
Cerebral hemorrhage	0.1 (1)	0.4 (4)	0.6 (1)	0.3 (4)

% (n)

Table 66 shows the temporal relationship of onset time for the first ARIA-E and ARIA-H in Studies 301 Core, 201 OLE, and 301 OLE. In concurrent ARIA-E and ARIA-H (cerebral microhemorrhage or superficial siderosis) cases occurring after the start of treatment with lecanemab, the majority of ARIA-H occurred at the same time or after the onset of ARIA-E. During the study period, ARIA-H without concurrent ARIA-E occurred sporadically.

Table 66. Temporal relationship of onset time for the first ARIA-E and ARIA-H in Study 201 OLE and Study 301 (Safety analysis set)

	301 Core		201 OLE	301 OLE[a]
	Placebo (N = 897)	Lecanemab (N = 898)	Received placebo during Core (N = 45)	Received placebo during Core (N = 714)
Subjects developing cerebral microhemorrhage	N = 68	N = 126	N = 5	N = 99
Without concurrent ARIA-E	92.6 (63)	47.6 (60)	80.0 (4)	36.4 (36)
With concurrent ARIA-E	7.4 (5)	52.4 (66)	20.0 (1)	63.6 (63)
Developed earlier than ARIA-E	2.9 (2)	6.3 (8)	0 (0)	4.0 (4)
Developed same day as ARIA-E	1.5 (1)	26.2 (33)	20.0 (1)	30.3 (30)
Developed later than ARIA-E	2.9 (2)	19.8 (25)	0 (0)	29 (29.3)
Subjects developing superficial siderosis	N = 21	N = 50	N = 1	N = 40
Without concurrent ARIA-E	61.9 (13)	46.0 (23)	100 (1)	32.5 (13)
With concurrent ARIA-E	38.1 (8)	54.0 (27)	0 (0)	67.5 (27)
Developed earlier than ARIA-E	0 (0)	2.0 (1)	0 (0)	0 (0)
Developed same day as ARIA-E	33.3 (7)	26.0 (13)	0 (0)	37.5 (15)
Developed later than ARIA-E	4.8 (1)	26.0 (13)	0 (0)	30.0 (12)

% (n)
a, Data with a cut-off date of December 1, 2022 were used.

Table 67 shows the list of subjects who developed ARIA-H (cerebral hemorrhage) in Studies 301 Core (lecanemab group), 201 OLE, and 301 OLE. In Study 301 Core, ARIA-H (cerebral hemorrhage) occurred in 6 subjects, with 3 of them being asymptomatic. In Studies 201 OLE and 301 OLE, ARIA-H (cerebral hemorrhage) occurred in 1 subject each, with 1 subject being asymptomatic. The outcomes of the 4 subjects who developed symptomatic ARIA-H (cerebral hemorrhage) were reported as either unresolved or resolving. The onset of ARIA-H (cerebral hemorrhage) was 34 to 441 days after the start of treatment with lecanemab. Of the 8 subjects who developed ARIA-H (cerebral hemorrhage), 3 subjects received anticoagulants and 3 subjects received antiplatelet drugs.

Table 67. List of subjects who developed ARIA-H (cerebral hemorrhage) in Studies 301 Core (lecanemab group), 201 OLE, and 301 OLE (Safety analysis set)

	Treatment during Core study	MCI /AD	Age (years)	Sex	Race	ApoE ε4 status	Onset (days)	Confirmed concomitant anticoagulant/ antiplatelet	Symptomatic/ severity/ symptom	Bleeding sites	Lecanemab treatment	Clinical outcome
301 Core	Lecanemab	AD	7[redacted]	[redacted]	[redacted]	Carrier	48	None/ticagrelor	Asymptomatic/ moderate	Right parietal, occipital	Interrupted	Not resolved
		AD	6[redacted]	[redacted]	[redacted]	Carrier	441	None/none	Symptomatic/ severe/language, left hemiplegia	Right cerebral hemisphere	Discontinued	Not resolved
		MCI	7[redacted]	[redacted]	[redacted]	Carrier	85	Rivaroxaban/ none	Symptomatic/ severe/left homonymous hemianopia, headache, convulsion	Right parietal	Interrupted	Resolving
		MCI	7[redacted]	[redacted]	[redacted]	Non-carrier	439	None/none	Symptomatic/ moderate/ abnormal behavior, language disorder	Left parietal lobe subcortical	Interrupted	Not resolved
		AD	7[redacted]	[redacted]	[redacted]	Carrier	175	Warfarin/aspirin	Asymptomatic/ mild	Right temporal, parietal lobe	Interrupted	Resolving
		AD	6[redacted]	[redacted]	[redacted]	Carrier	173	None/none	Asymptomatic/ mild	Right occipital lobe	Interrupted	Resolving
201 OLE	Placebo	MCI	7[redacted]	[redacted]	[redacted]	Non-carrier	34[a]	None/aspirin	Symptomatic/ moderate/right hemianopia	Left occipital	Interrupted	Not resolved
301 OLE	Placebo	AD	8[redacted]	[redacted]	[redacted]	Carrier	58[a]	Apixaban/none	Asymptomatic/ mild	Right temporal intraparenchymal	Discontinued	Resolved

a, Number of days after the start of OLE

(c) ARIA monitoring and whether to continue treatment in patients with ARIA

The applicant's explanation about the necessity of MRI monitoring for ARIA and its frequency:

To manage appropriately the important risk factor ARIA in the treatment with lecanemab and prevent ARIA events from becoming severe, examinations should be performed and evaluated carefully before and during administration of lecanemab to monitor closely for any MRI finding and any symptom by physicians with knowledge and experience in ARIA; therefore, cautionary statements to this effect will be included in the "Warning" section of the package insert. An increased incidence of ARIA was observed and the severity on imaging and clinical severity tended to be higher in homozygous *APOE4* carriers compared with non-carriers and heterozygous *APOE4* carriers. However, the onset of the first ARIA in homozygous *APOE4* carriers was similar to non-carriers and heterozygous *APOE4* carriers. Therefore, a cautionary statement to the effect that homozygous *APOE4* carriers have increased risk of ARIA, and implementing monitoring equivalent to that implemented for non-carriers and heterozygous *APOE4* carriers can assure patient safety.

Throughout the study period, ARIA-H without concurrent ARIA-E occurred in the lecanemab group sporadically at a similar level as in the placebo group in Study 301 Core; the time of onset of ARIA-H with

concurrent ARIA-E was similar to that of ARIA-E; therefore, MRI frequency after the start of lecanemab treatment was examined based on the onset profile of ARIA-E. The majority of the first ARIA-E events occurred within the first 6 months of treatment, and many of them occurred within the first 3 months (Table 58). Therefore, it is essential to perform MRI scans generally at Month 3 and up to Month 6. The incidence of the first ARIA-E in the lecanemab group after Month 6 to Month 12, and after Month 12 was low in all of the Studies 301 Core, 201 OLE, and 301 OLE, and no clear difference was observed compared with placebo in Study 301 Core. Accordingly, it is not necessary to include a cautionary statement to perform periodic MRI after Month 6. Instead, a cautionary statement to the effect that MRI should be performed as needed if any symptoms suggestive of ARIA appear will be included in the package insert to ensure the safety of patients.

If ARIA occurs after the start of lecanemab, whether to continue, interrupt, or discontinue treatment with lecanemab should be determined according to criteria similar to those for Study 301 (Table 39), and the patient should be monitored as shown below based on the type of ARIA, severity, and whether to continue treatment with lecanemab:

- If continuing lecanemab treatment after mild ARIA-E on imaging has occurred:

In Study 301 Core, among subjects who continued receiving treatment with lecanemab after mild ARIA-E on MRI occurred and subsequently ARIA became severe, the time in which ARIA became severe was within 1 to 2 months after the onset in the majority of cases; therefore, MRI should be planned 1 to 2 months after the onset of ARIA-E.

- If interrupting doses of lecanemab due to ARIA-E

The majority of ARIA-E events requiring interruption of lecanemab doses resulted in resolution on MRI within 2 to 4 months after the onset; therefore, when interrupting treatment due to onset of ARIA-E, perform MRI at 2 to 4 months after the onset of ARIA-E. If resolution is not confirmed on MRI, an additional MRI scan should be conducted.

- If ARIA-H with concurrent ARIA-E has occurred

Because ARIA-H and ARIA-E occurred during the same time period, implement MRI monitoring equivalent to that implemented after onset of ARIA-E.

- If continuing lecanemab treatment after ARIA-H without concurrent ARIA-E has occurred

The incidence of ARIA-H without concurrent ARIA-E in the lecanemab group was similar to that of the placebo group in Study 301 Core. When continuing lecanemab treatment after the onset of asymptomatic, mild ARIA-H on MRI, no special MRI is implemented, carefully monitor the course of ARIA-H, and if any symptom suggestive of ARIA is noted, perform MRI as necessary.

- If interrupting treatment due to ARIA-H without concurrent ARIA-E:

It is considered that ARIA-H requiring treatment interruption was stabilized 2 to 4 months after the onset of ARIA-H. Perform MRI at 2 to 4 months after the onset. If stabilization on MRI is not confirmed, perform an additional MRI scan.

In addition to the cautionary statements in the package insert mentioned above, the risk for ARIA associated with lecanemab can be properly managed by providing information using information materials for healthcare

professionals regarding ARIA, such as the occurrence of ARIA in the clinical studies, differential diagnosis method, and response to the onset of ARIA.

PMDA asked the applicant to explain the appropriateness of the inclusion of the patient population excluded from Studies 201 Core and 301 Core, that is, patients with evidence of vasogenic cerebral edema, 5 or more cerebral microhemorrhages, superficial siderosis, or >1 cm cerebral hemorrhages before the start of treatment.

The applicant's explanation:
Patients with evidence of vasogenic cerebral edema were excluded at the time of enrollment in Studies 201 Core and 301 Core; however, if ARIA-E was observed after the start of study drug treatment in Study 201 OLE and Study 301, the investigator could decide whether to continue study drug treatment according to the criteria in Tables 34 and 39, respectively [see Sections "7.2 Global phase II study" and "7.3 Global phase III study"]. This allowed experience in the lecanemab treatment of subjects with ARIA-E findings to be obtained. In Studies 201 OLE and 301 Core, of the 108 subjects in the lecanemab group who developed the first asymptomatic ARIA-E mild to moderate on MRI, 54 subjects continued treatment with lecanemab after the onset of ARIA-E. Of the 54 subjects, ARIA-E resolved in 34 subjects during the continued treatment. While 3 of the subjects had recurrent ARIA leading to treatment interruption, all subjects resumed lecanemab treatment after resolution of ARIA or stabilization on imaging. Of the subjects who continued treatment, treatment interruption occurred in 20 subjects ("worsened ARIA-E" [11 subjects], "worsened ARIA-E and onset/worsening of ARIA-H" [7 subjects], and "investigator's decision" [2 subjects]) and 18 of them resumed lecanemab treatment after resolution of ARIA-E. After resumption, 7 subjects experienced recurrent ARIA that led to treatment discontinuation or interruption, and 4 of them resumed treatment after interruption, with no ARIA leading to treatment discontinuation or interruption thereafter. Of the 898 subjects who received lecanemab in Study 301 Core, 28 subjects experienced recurrent ARIA-E, of whom 4 subjects had 3 recurrent ARIA-E events and 1 subject had 4 recurrent ARIA-E events.

Patients with evidence of ≥5 cerebral microhemorrhages, superficial siderosis, or >1 cm cerebral hemorrhages at the time of enrollment in Studies 201 Core and 301 Core were excluded from the studies. However, in Study 201 OLE and Study 301, the investigator could decide whether to continue study drug treatment in subjects who had ARIA-H according to the criteria in Tables 34 and 39, respectively [see Sections "7.2 Global phase II study" and "7.3 Global phase III study"]. In Studies 201 OLE and 301 OLE, except for symptomatic or worsened cases, enrollment was allowed even if cerebral microhemorrhages, superficial siderosis, or cerebral hemorrhages were observed. Although the number of subjects is small, experience in the initiation or continuation of lecanemab treatment in subjects with ARIA-H findings was obtained as shown in Table 68.

Table 68. Experience of treatment with lecanemab in subjects with superficial siderosis, ≥5 and <10 cerebral microhemorrhages, ≥10 cerebral microhemorrhages, or >1 cm cerebral hemorrhages in Study 201 OLE and Study 301

	Number of subjects with findings[a]	Action on study drug after onset
Asymptomatic, superficial siderosis without concurrent ARIA-E	39 subjects (including 18 subjects who had presented with findings at baseline)	Study drug treatment was continued without interruption, or initiated: 38 subjects After continuing or initiating treatment, experienced ARIA leading to treatment discontinuation or interruption: 9 subjects After the interruption above, resumed treatment after confirming stabilized findings on MRI: 3 subjects* *, Thereafter, no ARIA events leading to treatment discontinuation or interruption of lecanemab occurred. Study drug treatment was interrupted and after confirming stabilized findings on MRI, treatment was resumed with the presence of findings: 1 subject After resumption, no ARIA leading to study drug treatment discontinuation or interruption occurred.
Asymptomatic, ≥5 and <10 cerebral microhemorrhages without concurrent ARIA-E	15 subjects (including 6 subjects who had presented with findings at baseline)	Study drug treatment was continued without interruption, or initiated: 14 subjects After continuing or initiating treatment, experienced ARIA leading to treatment discontinuation or interruption: 3 subjects After the interruption above, resumed treatment after confirming stabilized findings on MRI: 1 subject* *, Thereafter, no ARIA events leading to treatment discontinuation or interruption of lecanemab occurred. Study drug treatment was interrupted and after confirming stabilized findings on MRI, treatment was resumed with the presence of findings: 1 subject After resumption, no ARIA leading to study drug treatment discontinuation or interruption occurred.
Asymptomatic, ≥10 cerebral microhemorrhages without concurrent ARIA-E	3 subjects	Study drug treatment was continued without interruption: 3 subjects After continuing treatment, ARIA-H (cerebral microhemorrhages) leading to study drug treatment discontinuation occurred in 1 subject. Treatment resumed after confirming stabilized findings on MRI, and completed treatment.
Asymptomatic, cerebral hemorrhages without concurrent ARIA-E	2 subjects	Study drug treatment was interrupted and then resumed with the presence of findings after confirming on MRI that findings had stabilized: 2 subjects After resumption, no ARIA leading to study drug treatment discontinuation or interruption occurred.

a, This does not include subjects who, after onset in Study 301 OLE, continued study drug treatment without interruption, or who resumed study drug treatment after interruption.

On the basis of the above results, while no study results on the initiation of treatment with lecanemab in patients with vasogenic cerebral edema are available, data have demonstrated a certain level of safety of lecanemab when treatment is continued in patients who presented with asymptomatic ARIA-E that is mild or moderate on MRI during treatment. Therefore, if the severity of vasogenic cerebral edema is mild or moderate on MRI and asymptomatic, it is considered possible to initiate treatment with lecanemab after careful consideration. Also, data have demonstrated a certain level of safety of lecanemab when treatment is initiated or continued in patients who have ARIA-H findings (≥5 cerebral microhemorrhages, superficial siderosis, or >1 cm cerebral hemorrhages), are asymptomatic and without concurrent ARIA-E. Therefore, it is possible to consider initiation of treatment with lecanemab after careful consideration if the patient is asymptomatic and concurrent vasogenic cerebral edema is absent. A cautionary statement to the effect that there is no experience in initiating treatment with lecanemab in patients who have ARIA-E and patients presenting with cerebral microhemorrhages (≥10) or cerebral hemorrhage will be included in the package insert.

(d) Relationship of the risk of ARIA with lecanemab and concomitant antithrombotic drugs

The applicant's explanation about the relationship between the risk of ARIA with lecanemab and concomitant antithrombotic drugs[49]:

Table 69 shows the incidence of ARIA by use of concomitant antiplatelet or anticoagulant drugs in Studies 301 and 201 OLE. There was no trend towards increasing risk of ARIA (ARIA-E or ARIA-H) by concomitant use of antiplatelet or anticoagulant drugs. Although the small number of patients experiencing cerebral hemorrhages precludes a strict evaluation of risk, the incidence of cerebral hemorrhages in the concomitant anticoagulant group was slightly higher compared with the non-concomitant group in the overall period of Studies 301 Core and OLE, while the incidence of cerebral hemorrhages in the concomitant antiplatelet group was slightly higher compared with the non-concomitant group in Study 201 OLE. Although the risk of cerebral hemorrhage in patients with AD using concomitant anticoagulants is not known, given that the use of anticoagulants alone is a risk factor for cerebral hemorrhage in a non-AD patient population, the relative contribution to the risk by lecanemab remains an open question. In view of the above, it is appropriate to include information on antithrombotic medications in the "Precautions Concerning Coadministration" section of the package insert to increase vigilance.

Table 69. Incidence of ARIA by use of concomitant antiplatelet or anticoagulant drugs in Studies 301 and 201 OLE (Safety analysis set)

	301		201 OLE[b]
	Core	Core + OLE	
	Placebo	Lecanemab[a]	Lecanemab[a]
ARIA-E			
No concomitant antiplatelet/anticoagulant	1.5 (9/586)	13.1 (134/1023)	8.0 (6/75)
Concomitant antiplatelet	0.84 (2/237)	12.9 (56/433)	8.1 (7/86)
Concomitant anticoagulant (including concomitant antiplatelet)	2.7 (2/74)	10.9 (17/156)	5.3 (1/19)
ARIA-H			
Cerebral microhemorrhage			
No concomitant antiplatelet/anticoagulant	7.2 (42/586)	15.3 (157/1023)	9.3 (7/75)
Concomitant antiplatelet	7.6 (18/237)	15.0 (65/433)	15.1 (13/86)
Concomitant anticoagulant (including concomitant antiplatelet)	9.5 (7/74)	12.8 (20/156)	21.1 (4/19)
Superficial siderosis			
No concomitant antiplatelet/anticoagulant	2.2 (13/586)	6.0 (61/1023)	2.7 (2/75)
Concomitant antiplatelet	2.1 (5/237)	4.8 (21/433)	7.0 (6/86)
Concomitant anticoagulant (including concomitant antiplatelet)	2.7 (2/74)	5.8 (9/156)	0 (0/19)
Cerebral hemorrhage			
No concomitant antiplatelet/anticoagulant	0 (0/586)	0.4 (4/1023)	0 (0/75)
Concomitant antiplatelet	0.4 (1/237)	0.2 (1/433)	1.2 (1/86)
Concomitant anticoagulant (including concomitant antiplatelet)	0 (0/74)	1.9 (3/156)[c]	0 (0/19)

% (n)

a, Data from subjects who received at least one dose of lecanemab 10 mg/kg biweekly regimen.

b, Data with cut-off date of December 1, 2022 were used.

c, Does not include 1 case of cerebral hemorrhage occurring >30 days after study drug treatment discontinuation and classified as non-TEAE.

[49] Antiplatelet drugs, anticoagulant drugs, and thrombolytic drugs

PMDA's view regarding Sections (a) though (d) above:
Amyloid-related imaging abnormalities are abnormal findings in brain imaging characteristic of anti-Aβ antibodies, and are classified into ARIA-E and ARIA-H. Although the pathological mechanism of ARIA is unclear, it is thought to be caused by an increase in brain vascular permeability caused by decomposition of accumulated Aβ in the cerebral blood vessels, inhibition of perivascular clearance by decomposition of Aβ in the cerebral parenchyma, and perivascular inflammation (*J Prev Alz Dis*. 2022;2:211-20). Since any irreversible damage to the brain by ARIA-E or ARIA-H may have serious effects on the prognosis of patients including cognitive function, monitoring for risk reduction and cautionary statements on necessary actions in the event of detecting ARIA are needed. For the risk management of ARIA, it is essential that lecanemab is used by physicians with adequate knowledge and experience at healthcare facilities where the required examinations can be performed. The applicant plans to include cautionary statements in the "Warning" section of the package insert to the effect that lecanemab should only be administered to patients who are determined to be eligible by physicians with sufficient knowledge and experience regarding the pathology, diagnosis, and treatment of AD and only at healthcare facilities capable of providing the examinations (including MRI) and risk management required for treatment with lecanemab, or at healthcare facilities coordinating with such healthcare facilities. The applicant's action above is appropriate.

As for the frequency of MRI, the applicant's explanation that MRI should be performed generally at Month 3 and up to Month 6, and the applicant's plan to provide cautionary statements regarding homozygous *APOE4* carrier patients are reasonable. However, given that there were reported cases of serious ARIA-E occurring ≥1 year after the start of treatment with lecanemab, continued vigilance is needed after Month 6 for onset of ARIA-E by closely observing for any change in neurological symptoms and by periodic brain MRI scans, based on the following:

- On the basis of the results from Studies 301 Core, 201 OLE, and 301 OLE, ARIA occurred more frequently within the first 6 months of treatment with lecanemab.
- The incidence of ARIA increased and the clinical and severity on MRI also tended to worsen with increasing number of ApoE ε4 alleles, while the onset time of ARIA was consistent irrespective of ApoE ε4 status.

In view of the applicant's explanation, it is reasonable to include in the package insert or other materials the recommended frequency of MRI scans in patients who develop ARIA after the start of treatment with lecanemab based on the type and severity of ARIA, and whether treatment should be continued.

In addition, an adequate brain MRI reading is essential for accurate diagnosis of ARIA, and therefore, a training program on reading MRIs should be implemented for healthcare professionals before using lecanemab.

The eligibility criteria for Studies 201 Core and 301 Core excluded enrollment of patients in whom vasogenic cerebral edema, ≥5 cerebral microhemorrhages, superficial siderosis, or >1 cm cerebral hemorrhages were noted before the start of treatment with lecanemab. PMDA concluded that lecanemab should be contraindicated

in patients with the conditions described above because no data have demonstrated that the risks are outweighed by the benefits based on the following.

- There are no safety data or only limited data when initiating treatment with lecanemab in the clinical studies in patients with the conditions described above.
- The applicant's explanation on the safety of lecanemab in patients with the conditions described above is primarily on the basis of safety data on patients who continued lecanemab following detection of ARIA-E or ARIA-H findings after the initiation of treatment with lecanemab in the clinical studies. Findings such as vasogenic cerebral edema before the initiation of treatment with lecanemab indicate the possibility that underlying diseases such as cerebral amyloid angiopathy and cerebral small vessel disease existed, and it cannot be determined whether the safety of lecanemab in such patients is similar to that in patients who develop ARIA-E or ARIA-H after treatment with lecanemab.

The appropriateness of the above conclusions by PMDA, and details of cautionary statements on ARIA will be finalized taking into account the comments from the Expert Discussion. Whether concomitant use of antithrombotic drugs is allowed should be considered based on the results of discussions in Section "7.R.4.2 Hemorrhagic events in the central nervous system."

7.R.4.2 Hemorrhagic events in the central nervous system

The applicant's explanation about the relationship between lecanemab and non-ARIA-H hemorrhagic events in the central nervous system (CNS):

Table 70 shows the incidence of non-ARIA-H CNS hemorrhagic events[50)] in Studies 301 Core, 201 OLE, and 301 OLE, and Table 71 shows the list of subjects who developed the events. The incidence of non-ARIA-H CNS hemorrhagic events in the lecanemab group in Study 301 Core is similar to that in the placebo group, and a causal relationship to lecanemab was denied for most of the events; therefore, lecanemab is not likely to increase the risk of non-ARIA-H CNS hemorrhagic events.

[50)] Two preferred terms (PTs) "subdural haematoma" and "subdural haemorrhage" were added to the CNS hemorrhagic events (adverse events reported using high level terms [HLT] "nervous system haemorrhagic disorders" and adverse events coded to PTs containing "haemorrhagic," "haematoma," or "haemosiderin" reported using HLT "Central nervous system haemorrhages and cerebrovascular accidents" or HLT "Central nervous system vascular disorders NEC") and events determined to be ARIA-H were excluded from the combined data for the analysis.

Table 70. Incidence of non-ARIA-H CNS hemorrhagic events[50)] in Studies 301 Core, 201 OLE, and 301 OLE (Safety analysis set)

	301 Core		201 OLE	301 OLE[b]
	Placebo (N = 897)	Lecanemab (N = 898)	Lecanemab (N = 180)	Lecanemab (N = 1385)
Non-ARIA-H hemorrhagic events in the nervous system	0.8 (7)	0.9 (8)	1.7 (3)	0.4 (5)
Amyloid related imaging abnormality-microhaemorrhages and haemosiderin deposits[a]	0.1 (1)	0 (0)	0 (0)	0 (0)
Subarachnoid haemorrhage	0.1 (1)	0.2 (2)	0 (0)	0 (0)
Superficial siderosis of central nervous system[a]	0.1 (1)	0 (0)	0 (0)	0 (0)
Haemorrhagic cerebral infarction	0 (0)	0 (0)	0 (0)	0.1 (1)
Thalamus haemorrhage[a]	0 (0)	0 (0)	0 (0)	0.1 (1)
Brain stem haemorrhage	0 (0)	0 (0)	0.6 (1)	0 (0)
Subdural haematoma	0.4 (4)	0.8 (7)	0.6 (1)	0.2 (3)
Subdural haemorrhage	0.1 (1)	0 (0)	0.6 (1)	0 (0)
Serious events	0.4 (4)	0.4 (4)	1.1 (2)	0.2 (3)
Death	0 (0)	0 (0)	0 (0)	0 (0)

% (n)

a, The event was not classified as ARIA-H.

b, Data with a cut-off date of December 1, 2022 were used.

Table 71. List of subjects who developed non-ARIA-H CNS hemorrhagic events[50] in Studies 301 Core (lecanemab group), 201 OLE, and 301 OLE (Safety analysis set)

	Treatment in Core study	MCI /AD	Age (years)	Sex	Race	ApoE ε4 status	Diagnosis	Onset (days)	Confirmed concomitant anticoagulant/ antiplatelet	Clinical severity	Clinical outcome	Lecanemab treatment	Relation
301 Core	Lecanemab	MCI	6[redacted]	[redacted]	[redacted]	Carrier	Subarachnoid haemorrhage (traumatic) Subdural haematoma	310 349	None/aspirin	Mild	Resolved	Continued	No
		AD	8[redacted]	[redacted]	[redacted]	Non-carrier	Subdural haematoma	359	None/aspirin	Severe	Resolved	Discontinued	No
		MCI	7[redacted]	[redacted]	[redacted]	Carrier	Subdural haematoma	127	None/none	Mild	Resolved	Interrupted	No
		MCI	9[redacted]	[redacted]	[redacted]	Carrier	Subdural haematoma	44[a] 66[b]	None/none	Severe[a] Mild[b]	Resolved[a] Resolved[b]	Interrupted[a] Interrupted[b]	No
		AD	7[redacted]	[redacted]	[redacted]	Carrier	Subdural haematoma	48	None/ ticagrelor	Mild	Resolved	Other[c]	No
		AD	7[redacted]	[redacted]	[redacted]	Carrier	Subdural haematoma	72	Rivaroxaban/ aspirin	Moderate	Resolved	Interrupted	No
		AD	8[redacted]	[redacted]	[redacted]	Carrier	Subdural haematoma	185	None/none	Mild	Resolved	Interrupted	No
		AD	7[redacted]	[redacted]	[redacted]	Carrier	Subarachnoid haemorrhage	79	None/aspirin	Mild	Resolved	Continued	Yes
201 OLE	Placebo	MCI	5[redacted]	[redacted]	[redacted]	Non-carrier	Subdural haemorrhage	23	None/none	Moderate	Resolved	Discontinued	No
	Lecanemab 5 mg/kg monthly	MCI	8[redacted]	[redacted]	[redacted]	Carrier	Brain stem haemorrhage	728	None/none	Mild	Unknown	Continued	No
	Lecanemab 5 mg/kg biweekly	AD	8[redacted]	[redacted]	[redacted]	Carrier	Subdural haematoma	897	Enoxaparin/ aspirin	Mild	Not resolved	Continued	No
301 OLE	Placebo	MCI	7[redacted]	[redacted]	[redacted]	Carrier	Thalamus haemorrhage	276	Heparin/none	Severe	Resolving	Discontinued	Yes
		MCI	6[redacted]	[redacted]	[redacted]	Carrier	Subdural haematoma	92[a] 106[b]	None/none	Mild[a] Severe[b]	Resolved (sequelae)[a] Resolving[b]	Interrupted[a] Interrupted[b]	Yes
	Lecanemab	AD	7[redacted]	[redacted]	[redacted]	Non-carrier	Subdural haematoma	632	None/none	Moderate	Resolved	Discontinued	No

a, First; b, Second; c, Interrupted due to other event

The tables below show the incidence of CNS hemorrhagic events including ARIA-H[51] by use or non-use of concomitant antithrombotic drug in Study 301 Core (Table 72) and Studies 301 OLE and 201 OLE (Table 73). Given that the incidence of CNS hemorrhagic events in subjects receiving lecanemab with concomitant antithrombotic drugs was similar to those without concomitant antithrombotic drugs and that a causal relationship to lecanemab was denied for most of the non-ARIA-H CNS hemorrhagic events, lecanemab is not likely to increase the risk for CNS hemorrhagic events in patients with ongoing antithrombotic treatment.

[51] Two PTs "subdural haematoma" and "subdural haemorrhage" were added to the CNS hemorrhagic events (adverse events reported using HLT "nervous system haemorrhagic disorders" and adverse events coded to PTs containing "haemorrhagic," "haematoma," or "haemosiderin" reported using HLT "Central nervous system haemorrhages and cerebrovascular accidents" or HLT "Central nervous system vascular disorders NEC") for the analysis.

Table 72. Incidence of CNS hemorrhagic events[51)] by use/non-use of concomitant antithrombotic drug in Study 301 Core (Safety analysis set)

	Concomitant antithrombotic		No concomitant antithrombic	
	Placebo (N = 312)	Lecanemab (N = 334)	Placebo (N = 585)	Lecanemab (N = 564)
Overall CNS hemorrhagic events	11.2 (35)	18.6 (62)	8.9 (52)	17.4 (98)
Amyloid related imaging abnormality-microhaemorrhages and haemosiderin deposits	8.7 (27)	14.1 (47)	7.2 (42)	14.0 (79)
Superficial siderosis of central nervous system	2.9 (9)	5.4 (18)	2.2 (13)	5.7 (32)
Cerebral haemorrhage	0 (0)	0.6 (2)	0 (0)	0.5 (3)
Haemorrhage intracranial	0.3 (1)	0 (0)	0 (0)	0 (0)
Thalamus haemorrhage	0 (0)	0 (0)	0 (0)	0 (0)
Subarachnoid haemorrhage	0 (0)	0.6 (2)	0.2 (1)	0 (0)
Brain stem haemorrhage	0 (0)	0 (0)	0 (0)	0 (0)
Haemorrhagic cerebral infarction	0 (0)	0 (0)	0 (0)	0 (0)
Subdural haematoma	0.6 (2)	1.2 (4)	0.3 (2)	0.5 (3)
Subdural haemorrhage	0 (0)	0 (0)	0.2 (1)	0

% (n)

Table 73. Incidence of CNS hemorrhagic events[51)] by use/non-use of concomitant antithrombotic drug in Studies 201 OLE and 301 OLE (Safety analysis set)

	201 OLE		301 OLE[a]			
	Concomitant antithrombic	No concomitant antithrombic	Concomitant antithrombic		No concomitant antithrombic	
	Lecanemab (N = 111)	Lecanemab (N = 69)	Placebo[b] (N = 241)	Lecanemab[b] (N = 247)	Placebo[b] (N = 473)	Lecanemab[b] (N = 424)
Overall CNS hemorrhagic events	19.8 (22)	14.5 (10)	17.4 (42)	9.3 (23)	14.8 (70)	10.6 (45)
Amyloid related imaging abnormality-microhaemorrhages and haemosiderin deposits	15.3 (17)	10.1 (7)	15.8 (38)	8.9 (22)	12.9 (61)	9.0 (38)
Superficial siderosis of central nervous system	5.4 (6)	2.9 (2)	6.6 (16)	0.8 (2)	5.1 (24)	1.2 (5)
Cerebral haemorrhage	0.9 (1)	0 (0)	1.2 (3)	0 (0)	0 (0)	0 (0)
Haemorrhage intracranial	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Thalamus haemorrhage	0 (0)	0 (0)	0.4 (1)	0 (0)	0 (0)	0 (0)
Subarachnoid haemorrhage	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Brain stem haemorrhage	0 (0)	1.4 (1)	0 (0)	0 (0)	0 (0)	0 (0)
Haemorrhagic cerebral infarction	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0.2 (1)
Subdural haematoma	0.9 (1)	0 (0)	0 (0)	0 (0)	0.2 (1)	0.2 (1)
Subdural haemorrhage	0 (0)	1.4 (1)	0 (0)	0 (0)	0 (0)	0 (0)

% (n)
a, Data with a cut-off date of December 1, 2022 were used except for the data on subdural haematoma and subdural haemorrhage
b, Treatment in the Core study

PMDA asked the applicant to explain whether lecanemab may increase the risk of developing cerebral hemorrhage in patients with risk factors for cerebral hemorrhage such as hypertension (*Guideline for the treatment of stroke* 2021. Kyowa Kikaku, Ltd.;2021, *N Engl J Med.* 2022;387:1589-96).

The applicant's explanation:

Tables 74 and 75 show the incidence of CNS hemorrhagic events including ARIA-H[51)] by the presence of hypertension. The overall incidence of CNS hemorrhagic events was similar between the subgroups based on

the presence or absence of hypertension, and there was no significant difference in the incidence of each event. Similar analyses were conducted for other risk factors of cerebral hemorrhage, namely, diabetes mellitus, cardiac disease, obesity, and sleep apnea syndrome. The results showed that the overall incidence of CNS hemorrhagic events was consistent between the subgroups based on the presence or absence of each factor. Therefore, lecanemab is not likely to increase the likelihood of CNS hemorrhagic events in patients with risk factors for cerebral hemorrhage.

Table 74. Incidence of CNS hemorrhagic events[51)] by the presence of hypertension in Study 301 Core (Safety analysis set)

	Hypertension		No hypertension	
	Placebo (N = 499)	Lecanemab (N = 491)	Placebo (N = 398)	Lecanemab (N = 407)
Overall CNS hemorrhagic events	10.6 (53)	17.3 (85)	8.5 (34)	18.4 (75)
Amyloid related imaging abnormality-microhaemorrhages and haemosiderin deposits	8.8 (44)	13.8 (68)	6.3 (25)	14.3 (58)
Superficial siderosis of central nervous system	2.0 (10)	4.1 (20)	3.0 (12)	7.4 (30)
Cerebral haemorrhage	0 (0)	0.6 (3)	0 (0)	0.5 (2)
Haemorrhage intracranial	0.2 (1)	0 (0)	0 (0)	0 (0)
Thalamus haemorrhage	0 (0)	0 (0)	0 (0)	0 (0)
Subarachnoid haemorrhage	0 (0)	0.4 (2)	0.3 (1)	0 (0)
Brain stem haemorrhage	0 (0)	0 (0)	0 (0)	0 (0)
Haemorrhagic cerebral infarction	0 (0)	0 (0)	0 (0)	0 (0)
Subdural haematoma	0.6 (3)	1.0 (5)	0.3 (1)	0.5 (2)
Subdural haemorrhage	0 (0)	0 (0)	0.3 (1)	0 (0)

% (n)

Table 75. Incidence of CNS hemorrhagic events[51)] by the presence of hypertension in Studies 201 OLE and 301 OLE (Safety analysis set)

	201 OLE		301 OLE[a]			
	Hypertension	No hypertension	Hypertension		No hypertension	
	Lecanemab[b] (N = 104)	Lecanemab[b] (N = 76)	Placebo[c] (N = 380)	Lecanemab[c] (N = 355)	Placebo[c] (N = 334)	Lecanemab[c] (N = 316)
Overall CNS hemorrhagic events	22.1 (23)	11.8 (9)	15.0 (57)	11.5 (41)	16.8 (56)	8.5 (27)
Amyloid related imaging abnormality-microhaemorrhages and haemosiderin deposits	16.3 (17)	9.2 (7)	13.2 (50)	10.7 (38)	14.7 (49)	7.0 (22)
Superficial siderosis of central nervous system	5.8 (6)	2.6 (2)	5.0 (19)	0.8 (3)	6.3 (21)	1.3 (4)
Cerebral haemorrhage	1.0 (1)	0 (0)	0.5 (2)	0 (0)	0.3 (1)	0 (0)
Haemorrhage intracranial	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Thalamus haemorrhage	0 (0)	0 (0)	0.3 (1)	0 (0)	0 (0)	0 (0)
Subarachnoid haemorrhage	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Brain stem haemorrhage	1.0 (1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Haemorrhagic cerebral infarction	0 (0)	0 (0)	0 (0)	0.3 (1)	0 (0)	0 (0)
Subdural haematoma	1.0 (1)	0 (0)	0.3 (1)	0 (0)	0.3 (1)	0.3 (1)
Subdural haemorrhage	0 (0)	1.3 (1)	0 (0)	0 (0)	0 (0)	0 (0)

% (n)

a, Data with a cut-off date of December 1, 2022 were used

b, Since there were only a few subjects who had been assigned to placebo in the Core study, data were analyzed without dividing into treatment groups of the Core study.

c, Indicates treatment in the Core study

Given that East Asian populations tend to have a higher incidence of cerebral hemorrhage (*N Engl J Med.* 2022;387:1589-96), PMDA asked the applicant to explain whether it is likely that the incidence of cerebral hemorrhage is higher in Asian populations including Japanese than in non-Asian populations in patients taking lecanemab.

The applicant's explanation:

The tables below show the incidence of CNS hemorrhagic events including ARIA-H[51)] by race (Asian or non-Asian) in Study 301 Core (Table 76) and Studies 201 OLE and 301 OLE (Table 77). The overall incidence of CNS hemorrhagic events was similar between non-Asian and Asian populations, suggesting that the risk of developing CNS hemorrhagic events is similar between Asian (including Japanese) and non-Asian populations in patients taking lecanemab.

Table 76. Incidence of CNS hemorrhagic events[51)] by race in Study 301 Core (Safety analysis set)

	Asian		Non-Asian	
	Placebo (N = 150)	Lecanemab (N = 153)	Placebo (N = 747)	Lecanemab (N = 745)
Overall CNS hemorrhagic events	16.0 (24)	15.7 (24)	8.4 (63)	18.3 (136)
Amyloid related imaging abnormality-microhaemorrhages and haemosiderin deposits	14.7 (22)	10.5 (16)	6.3 (47)	14.8 (110)
Superficial siderosis of central nervous system	4.0 (6)	4.6 (7)	2.1 (16)	5.8 (43)
Cerebral haemorrhage	0 (0)	0.7 (1)	0 (0)	0.5 (4)
Haemorrhage intracranial	0 (0)	0 (0)	0.1 (1)	0 (0)
Thalamus haemorrhage	0 (0)	0 (0)	0 (0)	0 (0)
Subarachnoid haemorrhage	0 (0)	0.7 (1)	0.1 (1)	0.1 (1)
Brain stem haemorrhage	0 (0)	0 (0)	0 (0)	0 (0)
Haemorrhagic cerebral infarction	0 (0)	0 (0)	0 (0)	0 (0)
Subdural haematoma	0 (0)	2.0 (3)	0.5 (4)	0.5 (4)
Subdural haemorrhage	0 (0)	0 (0)	0.1 (1)	0 (0)

% (n)

Table 77. Incidence of CNS hemorrhagic events[51)] by race in Studies 201 OLE and 301 OLE (Safety analysis set)

	201 OLE		301 OLE[a]			
	Asian	Non-Asian	Asian		Non-Asian	
	Lecanemab[b] (N = 30)	Lecanemab[b] (N = 150)	Placebo[c] (N = 129)	Lecanemab[c] (N = 125)	Placebo[c] (N = 585)	Lecanemab[c] (N = 546)
Overall CNS hemorrhagic events	16.7 (5)	18.0 (27)	14.7 (19)	8.0 (10)	16.1 (94)	10.6 (58)
Amyloid related imaging abnormality-microhaemorrhages and haemosiderin deposits	13.3 (4)	13.3 (20)	11.6 (15)	6.4 (8)	14.4 (84)	9.5 (52)
Superficial siderosis of central nervous system	3.3 (1)	4.7 (7)	7.0 (9)	1.6 (2)	5.3 (31)	0.9 (5)
Cerebral haemorrhage	0 (0)	0.7 (1)	0 (0)	0 (0)	0.5 (3)	0 (0)
Haemorrhage intracranial	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Thalamus haemorrhage	0 (0)	0 (0)	0.8 (1)	0 (0)	0 (0)	0 (0)
Subarachnoid haemorrhage	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Brain stem haemorrhage	0 (0)	0.7 (1)	0 (0)	0 (0)	0 (0)	0 (0)
Haemorrhagic cerebral infarction	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0.2 (1)
Subdural haematoma	0 (0)	0.7 (1)	0 (0)	0 (0)	0.3 (2)	0.2 (1)
Subdural haemorrhage	0 (0)	0.7 (1)	0 (0)	0 (0)	0 (0)	0 (0)

% (n)
a, Data with a cut-off date of December 1, 2022 were used
b, Since there were only a few subjects who had been assigned to placebo in the Core study, data were analyzed without dividing into treatment groups of the Core study.
c, Indicates treatment in the Core study

PMDA asked the applicant to explain the details of subjects who were confirmed to have died after the data cut-off date for Study 301 OLE (April 15, 2022).

The applicant's explanation:
Table 78 shows the details of 2 subjects who died after the data cut-off date for Study 301 OLE (April 15, 2022).

Table 78. List of subjects who died after the data cut-off date for Study 301 OLE (Safety analysis set)

MCI /AD	Age (years)	Sex	Race	ApoE ε4 status	Treatment in Core study	Diagnosis	Onset[a] (days)	Confirmed concomitant antithrombotic	Clinical severity	Bleeding site
MCI	63	Female	White	Carrier	Placebo	Cerebral hemorrhage	37	Thrombolytic drug	Severe	Multiple
MCI	85	Male	White	Non-carrier	Placebo	Cerebral hemorrhage	143	Aspirin Apixaban Heparin	Severe	Left occipital lobe

a, Days after the start of OLE

One of the subjects presented with multiple cerebral hemorrhage after receiving a thrombolytic drug for the treatment of cerebral infarction, and was later confirmed to have died. The autopsy results are shown below. Of the findings, histiocytic necrotizing vasculitis accompanied by plaque phagocytosis and brain parenchymal microglial response were suggested to be a host response to the anti-Aβ therapy. Multiple cerebral hemorrhage was reported to be related to the study drug by the investigator; however, intracerebral hemorrhage is not considered related to lecanemab by the sponsor because vasculitis is reported in patients with cerebral amyloid angiopathy irrespective of anti-Aβ therapies (*Arthritis Rheum.* 2003;49:421-7, *Semin Arthritis Rheum.*

2014;44:86-92) and there have been reports of cases of intracerebral hemorrhage after thrombolytic therapy (*J Neurol Transl Neurosci.* 2014;2:1034).

- Alzheimer's disease neuropathological changes
- Multifocal cortical intracerebral hemorrhage in the bilateral cerebral hemisphere
- Cortical histiocytic vasculitis with fibrinoid necrosis
- Cerebral amyloid angiopathy with histiocytic response
- Histiocytic/microglial response to parenchymal amyloid plaques

The other subject underwent brain scan after a fall, which revealed intracerebral hemorrhage in the left occipital lobe, and apixaban therapy was interrupted. Later, this subject developed myocardial infarction and was treated with heparin. Subsequently, the subject was admitted to the hospice and confirmed to have died. The autopsy results showed intracerebral hemorrhage in the left occipital lobe and subarachnoid hemorrhage caused by traumatic falling; however, it was concluded that the cause of death was not in the brain. Therefore, although a causal relationship to lecanemab could not be ruled out for intracerebral hemorrhage, lecanemab is not considered to be related to the death.

PMDA's view:

On the basis of the applicant's explanation, lecanemab is unlikely to increase the risk of incidence of non-ARIA-H CNS hemorrhagic events. The results of subgroup analyses showed that lecanemab did not significantly increase the incidence of CNS hemorrhagic events in patients with increased risk factors for cerebral hemorrhage such as hypertension and that the incidence of CNS hemorrhagic events was not affected by race; therefore, it is unlikely that the risk of incidence of CNS hemorrhagic events including ARIA-H by lecanemab differs between the presence and absence of risk factor for cerebral hemorrhage or between the races.

While patients on concomitant antithrombotic medication should be monitored closely for cerebral hemorrhage when using lecanemab considering the factors shown below, no clinically unacceptable risks have been identified at present. The applicant's plan to include antithrombotic drugs in the "Precautions Concerning Coadministration" section of the package insert to increase vigilance is appropriate. However, information on the patient who had received antithrombotic medication concurrently with lecanemab and subsequently died should be provided in an appropriate manner using information materials.

- Although the overall incidence of CNS hemorrhagic events including ARIA-H was similar between subjects with and without concomitant antithrombotic medication, the incidence of ARIA-H (cerebral hemorrhage) tended to be higher in subjects with concomitant antithrombotic medication [see Section "7.R.4.1 Amyloid-related imaging abnormalities"].
- There were 2 cases of cerebral hemorrhage in which subjects had received concomitant antithrombic medication during treatment with lecanemab and which resulted in death. It is considered difficult to clearly deny the possibility that a causal relationship might have existed between cerebral hemorrhage and lecanemab in one of the subjects (female 63 years of age).

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

7.R.4.3 Infusion reaction

The applicant's explanation about infusion reaction[52]:

In Studies 201 and 301, subjects were allowed to receive prophylactic medications before administration of the next dose of the study drug to prevent an immune response and infusion reactions after the investigator had evaluated subject's immune response to the study drug based on the clinical findings and laboratory results [see Sections "7.2 Global phase II study" and "7.3 Global phase III study"]. In Study 201 OLE, only 1 subject who received placebo in the Core study experienced infusion reactions multiple times; therefore, investigations in the following paragraphs are based on the results of Study 301.

Tables 79 and 80 show infusion reactions that occurred in Studies 301 Core and 301 OLE, respectively. The incidence of infusion reactions in Study 301 Core was higher in the lecanemab group than in the placebo group and most of the events were mild or moderate in severity. Infusion reactions classified into NCI-CTCAE Grade 3 or 4 occurred in 7 subjects in the lecanemab group. While all 7 subjects required intensive management at secondary medical institutions, all recovered within 1 to 4 days after onset except for 1 subject. No events resulted in death. There was no clear relationship between the occurrence of infusion events and the presence of ADA (in Study 301 Core, the incidence of infusion reaction was 30.6% [15 of 49 subjects] in ADA-positive subjects; 28.4% [122 of 429 subjects] in ADA-negative subjects; in Study 301 OLE, 30.0% [15 of 50 subjects] in ADA-positive subjects; 28.6% [127 of 444 subjects] in ADA-negative subjects).

Table 79. Incidence of infusion reaction[52] in Study 301 Core (Safety analysis set)

	Overall		Without prophylaxis medications		With prophylaxis medications	
	Placebo (N = 897)	Lecanemab (N = 898)	Placebo (N = 855)	Lecanemab (N = 773)	Placebo (N = 42)	Lecanemab (N = 125)
Infusion reaction any grade	7.4 (66)	26.4 (237)	6.7 (57)	17.7 (137)	21.4 (9)	80.0 (100)
Category						
Grade 1[a]	4.6 (41)	8.7 (78)	4.7 (40)	9.3 (72)	2.4 (1)	4.8 (6)
Grade 2[a]	2.8 (25)	16.6 (149)	2.0 (17)	7.4 (57)	19.0 (8)	73.6 (92)
Grade 3[a]	0 (0)	0.7 (6)	0 (0)	0.6 (5)	0 (0)	0.8 (1)
Grade 4[a]	0 (0)	0.1 (1)	0 (0)	0.1 (1)	0 (0)	0 (0)
Grade 5[a]	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Missing	0 (0)	0.3 (3)	0 (0)	0.3 (2)	0 (0)	0.8 (1)
Serious events	0 (0)	1.2 (11)	—	—	—	—
Treatment discontinuation	0.1 (1)	1.3 (12)	—	—	—	—

% (n)

a, NCI-CTCAE Grade

[52] Medical dictionary for regulatory activities (MedDRA) PTs "infusion related reaction" and "infusion site reaction"

Table 80. Incidence of infusion reaction[52] in Study 301 OLE (Safety analysis set)

	Overall (Core + OLE)	Without prophylaxis medications	With prophylaxis medications
	Lecanemab (N = 1391)	Lecanemab (N = 1195)	Lecanemab (N = 196)
Infusion reaction any grade	24.2 (336)	16.0 (191)	74.0 (145)
Category			
Grade 1[a]	8.0 (111)	7.9 (94)	8.7 (17)
Grade 2[a]	15.3 (213)	7.3 (87)	64.3 (126)
Grade 3[a]	0.5 (7)	0.5 (6)	0.5 (1)
Grade 4[a]	0.1 (1)	0.1 (1)	0 (0)
Grade 5[a]	0 (0)	0 (0)	0 (0)
Missing	0.3 (4)	0.3 (3)	0.5 (1)
Serious events	1.3 (18)	—	—
Treatment discontinuation	1.3 (18)	—	—

% (n)
a, NCI-CTCAE Grade

The recurrence of infusion reactions with and without prophylactic medications prior to the next administration of lecanemab after an infusion reaction occurred at the initial administration in the lecanemab group in Study 301 Core was investigated. The infusion reaction recurrence rate was lower in the group with prophylactic medications than in the group without (25.6% and 42.1%, respectively). Therefore, it is advisable to include a cautionary statement in the package insert to the effect that prophylactic medications prior to next administration should be considered in patients who experienced an infusion reaction at the initial administration.

PMDA's view:
On the basis of the submitted data from the clinical studies, the incidence of infusion reactions is higher in the lecanemab group than in the placebo group, with some being Grade ≥3 requiring hospitalization; therefore, infusion reaction should be cautioned as a clinically significant adverse reaction while sufficient information including the details of events that occurred in the clinical studies and actions to be taken in response to the onset of infusion reaction should be provided using information materials. In view of the applicant's explanation, it is appropriate to include a cautionary statement in the package insert to the effect that administration of premedication such as an antihistamine should be considered prior to the next administration of lecanemab if patients experienced an infusion reaction at the initial administration. The appropriateness of the decision above will be finalized taking into account the comments from the Expert Discussion.

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

The applicant's explanation about nervous system-related adverse events[53]:
Table 81 shows nervous system-related adverse events that occurred in Studies 301 Core, 201 OLE, and 301 OLE. In Study 301 Core, besides ARIA, the incidence of headache was higher in the lecanemab group than in the placebo group. The incidence of the other events was similar between lecanemab and placebo. In view of the above, nervous system-related adverse events excluding ARIA should be described in the "Other adverse reactions" section of the package insert. Nervous system-related adverse events that are likely to occur in

[53] Adverse events classified as MedDRA system organ class (SOC) "nervous system disorders."

association with ARIA should be indicated as symptoms associated with ARIA in the "Clinically significant adverse reactions" section to increase vigilance.

Table 81. Incidence of nervous system-related adverse events[53)] in Studies 201 and 301 (Safety analysis set)

	301 Core		OLE	
	Placebo (N = 897)	Lecanemab (N = 898)	Study 201 (N = 180)	Study 301 (Core + OLE) (N = 1391)
Nervous system-related adverse events	32.4 (291)	43.5 (391)	46.7 (84)	38.0 (528)
Main events[a]				
Amyloid related imaging abnormality-microhaemorrhages and haemosiderin deposits	7.7 (69)	14.0 (126)	13.3 (24)	12.8 (178)
Amyloid related imaging abnormality-oedema/effusion	1.7 (15)	12.6 (113)	7.8 (14)	11.9 (166)
Headache	8.1 (73)	11.1 (100)	8.9 (16)	9.4 (131)
Superficial siderosis of central nervous system	2.5 (22)	5.6 (50)	4.4 (8)	4.8 (67)
Dizziness	5.1 (46)	5.5 (49)	6.7 (12)	4.7 (65)
Syncope	1.3 (12)	2.0 (18)	2.2 (4)	1.6 (22)
Serious events	1.7 (15)	3.3 (30)	6.1 (11)	2.9 (41)
Study drug treatment discontinuation	0.9 (8)	3.2 (29)	0 (0)	2.6 (36)

% (n)
a, Adverse events occurring in ≥2% of subjects in the lecanemab group of Study 301 Core

PMDA's view:
Some nervous system-related adverse events may occur in association with ARIA, and presence of these events offers important information for early detection of ARIA and for what actions to take. The applicant's plan to describe the symptoms of nervous system-related adverse events associated with ARIA in the "Clinically significant adverse reactions" section is appropriate.

7.R.4.5 Psychiatric disorders (including suicidal behaviour, suicidal ideation)

The applicant's explanation about psychiatric disorder-related adverse events[54)]:
Table 82 shows psychiatric disorder-related adverse events that occurred in Studies 301 Core, 201 OLE, and 301 OLE. The incidence of psychiatric disorder-related adverse events in the lecanemab group in Study 301 Core was similar to that in the placebo group. In Study 301 Core, suicide attempt was reported in 1 subject in the lecanemab group, and a causal relationship to the study drug was denied for the event. In Studies 201 Core and 301 Core, the proportion of subjects whose Columbia Suicide Severity Rating Scale (C-SSRS) score became worse than that at baseline was similar between lecanemab and placebo. Therefore, no special cautionary statement is necessary for psychiatric disorder-related adverse events, and the events should be included in the "Other adverse reactions" section to increase vigilance.

54) Adverse events classified as MedDRA SOC "psychiatric disorders"

Table 82. Incidence of psychiatric disorder-related adverse events[54)] in Studies 201 and 301 (Safety analysis set)

	301 Core		OLE	
	Placebo (N = 897)	Lecanemab (N = 898)	Study 201 (N = 180)	Study 301 (Core + OLE) (N = 1391)
Psychiatric disorder-related adverse events	17.5 (157)	15.8 (142)	26.7 (48)	13.7 (190)
Main events[a]				
Anxiety	4.2 (38)	5.0 (45)	7.8 (14)	4.2 (59)
Insomnia	2.3 (21)	2.7 (24)	2.2 (4)	2.2 (31)
Depression	4.2 (38)	2.6 (23)	6.1 (11)	2.3 (32)
Serious events	0.7 (6)	0.3 (3)	1.1 (2)	0.4 (5)
Study drug treatment discontinuation	0.1 (1)	0.3 (3)	0.6 (1)	0.1 (2)

% (n)
a, Adverse events occurring in ≥2% of subjects in the lecanemab group of Study 301 Core

PMDA's view:
No clear concerns have been raised regarding psychiatric disorders such as suicidal behaviour and suicidal ideation associated with lecanemab, and the applicant's plan to describe psychiatric disorder-related adverse events in the "Other adverse reactions" section of the package insert is appropriate. However, in addition to the nervous system-related adverse events described in Section 7.R.4.4 above, some psychiatric disorder-related adverse events such as confusional state and hallucination may also emerge as symptoms associated with ARIA. Therefore, such symptoms should be indicated as symptoms associated with ARIA in the "Clinically significant adverse reactions" section to increase vigilance.

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

The applicant's explanation about the intended patient population of lecanemab:
Studies 201 and 301 were conducted in patients with early AD. These patients needed to meet the NIA-AA core clinical criteria for MCI due to AD or mild AD-D, have a global CDR score of 0.5 to 1, and a Memory Box score of ≥0.5, MMSE score of 22 to 30, and have findings suggestive of Aβ pathology. The data demonstrated the efficacy of lecanemab for the intended patient population in slowing the worsening of clinical symptoms, reducing Aβ accumulation in the brain, and improving tau pathology and the neurodegenerative process, and these effects appeared to be maintained after the completion of treatment with lecanemab. It is considered that the observed efficacy was the result of the mechanism of action of lecanemab, which modifies and inhibits the pathophysiology of AD, and therefore, "to slow the progression of mild cognitive impairment and mild dementia due to Alzheimer's disease" is appropriate as the indication of lecanemab.

In Study 301 Core, the Aβ pathology of subjects was examined based on the amyloid PET results at screening or from the past, or CSF assessment at screening. PMDA asked the applicant to explain whether patients intended for lecanemab treatment can be selected appropriately by either assessment method.

The applicant's explanation:
Table 83 shows the results for the primary endpoint, the change from baseline in CDR-SB at Month 18 in Study 301 Core obtained by the method used to assess Aβ pathology at screening. In subjects enrolled based on amyloid PET assessment, CDR-SB decline was slowed in the lecanemab group compared with placebo; in

contrast, in subjects enrolled based on CSF assessment, slowing of CDR-SB decline by lecanemab compared with placebo was not observed. Among subjects enrolled based on CSF assessment, those assigned to placebo had a low adjusted mean difference from baseline in CDR-SB at Month 18; in addition, the number of subjects enrolled based on CSF assessment was small. These factors may have made it difficult to detect the difference between the lecanemab and placebo groups.

Table 83. Change from baseline in CDR-SB in Study 301 Core by assessment method for Aβ pathology (FAS+)

	Amyloid PET[55)]		Past amyloid PET[56)]		CSF[57)]	
	Placebo	Lecanemab	Placebo	Lecanemab	Placebo	Lecanemab
Baseline (Mean ± standard deviation)	N = 566 3.24 ± 1.377	N = 568 3.23 ± 1.331	N = 47 3.04 ± 1.155	N = 45 2.82 ± 1.149	N = 119 3.03 ± 1.298	N = 126 2.88 ± 1.395
Change from baseline at Month 18 (MMRM) (Adjusted mean ± standard error)	N = 494 1.580 ± 0.093	N = 470 1.113 ± 0.094	N = 40 2.088 ± 0.406	N = 41 1.456 ± 0.405	N = 106 1.086 ± 0.200	N = 107 1.324 ± 0.196
Adjusted mean difference between groups	—	−0.467	—	−0.631	—	0.239

It has been reported that CSF levels are highly correlated with pathology findings on brain amyloid from autopsy and with amyloid PET (*Ann Neurol.* 2009;65:403-13, *Clinical Guidelines on the Proper Use of Cerebrospinal Fluid and Blood Biomarkers for Dementia.* [in Japanese] Research group under Grants-in-Aid for Scientific Research;2021), and that the t-tau/Aβ (1-42) ratio in CSF, used in CSF measurement at screening in Study 301, is in high agreement (91.1%) with amyloid PET by visual read (*Alzheimers Dement.* 2023; Online ahead of print). The agreement with the results of visual read was 83% in subjects who underwent both CSF measurement and amyloid PET at screening for entry into Study 301. However, after having tested negative for amyloid by CSF or amyloid PET, some subjects wished to participate in the clinical trial and underwent the other assessment, some of whom tested positive. Consequently, the observed agreement was slightly lower than the agreement which would be obtained from cases where no previous assessment result for Aβ pathology is available. In view of the relationship of assessment methods, while the majority of the subjects who were enrolled based on the CSF results had not undergone amyloid PET measurements, most of them were presumably positive for amyloid PET. In fact, the patient characteristics of subjects who were enrolled based on the CSF results were roughly similar to those of the overall population. Furthermore, the values showing the change from baseline in CDR-SB at Month 18 in the placebo group of subjects who were enrolled in the study based on the CSF results were distributed within the range of values of subjects who were enrolled in the study based on the results of amyloid PET assessment, suggesting that the subjects enrolled based on CSF and those enrolled based on amyloid PET had similar characteristics. Currently, the number of facilities capable of providing amyloid PET are limited, and lumbar puncture performed for CSF sampling is contraindicated in some patients. Given these and other factors, it is difficult to limit assessment methods to just one technique, amyloid PET or CSF, as the Aβ pathology in all patients needs to be confirmed.

55) Subjects who tested positive for amyloid PET or CSF in the past were excluded.
56) Subjects who tested positive for amyloid PET or CSF at screening were excluded.
57) Subjects who tested positive for amyloid PET at screening or in the past were excluded.

On the basis of the above, patients intended for lecanemab should be defined as those in whom Aβ pathology is confirmed by amyloid PET, CSF, or testing methods of equivalent accuracy in clinical settings. The "Precautions concerning indications" section of the package insert should include, in addition to the assessments required in the selection of intended patients described above, cautionary statements to the effect that patients intended for lecanemab treatment should be selected based on factors including the efficacy expected with lecanemab, the inclusion criteria in the clinical studies, and result data from the clinical studies.

PMDA's view:
Among patients with AD, those who were eligible for enrollment in the clinical studies of lecanemab and in whom lecanemab has been demonstrated to have efficacy are patients with "mild cognitive impairment and mild dementia due to Alzheimer's disease"; therefore, the intended patient population proposed by the applicant is appropriate. With regard to the efficacy expected from treatment with lecanemab, it cannot be concluded that the disease-modifying effect of lecanemab has been verified based on the submitted clinical study result data for the following reasons: although the clinical study data demonstrated the effect of lecanemab on slowing the progression of symptoms and efficacy on biomarkers associated with Aβ pathology, the efficacy verified was the primary endpoint associated with clinical symptoms. The relationship between the effect of slowing the progression of clinical symptoms and change in each biomarker has not been sufficiently clarified [see Section "7.R.3.3 Biomarkers"]. Therefore, the indication should be "to slow the progression of mild cognitive impairment due to Alzheimer's disease and mild dementia of the Alzheimer type."

In Study 301 Core, the efficacy results in subjects who were enrolled in the study based on the CSF-positive result differed from those who were enrolled in the study based on the amyloid PET-positive result. The applicant's explanation has not clarified what caused the difference between the assessment methods for Aβ pathology. However, based on the applicant's explanation about the correlation of CSF and PET assessment methods, patients selected by CSF assessment are similar to those selected by amyloid PET; therefore, the applicant's proposal of confirming Aβ pathology by amyloid PET, CSF, or testing method of equivalent accuracy is reasonable.

The intended patient population should be clarified before using lecanemab in clinical settings, and at least the following cautionary statements should be provided in the "Precautions concerning indication" section or by other means to communicate accurate information on the efficacy that can be expected with lecanemab treatment and to facilitate selection of intended patients.

- Lecanemab is not intended to completely stop the progression of or cure mild cognitive impairment due to Alzheimer's disease and mild dementia of the Alzheimer type.
- Whether to administer lecanemab to patients should be determined only after the diagnostic criteria, the range of clinical symptom scores, exclusion criteria and other information used in Study 301 Core are fully understood.
- The Aβ pathology should be confirmed by amyloid PET or CSF biomarker as used in Study 301 Core, or by testing methods of equivalent or more accuracy.

- The efficacy and safety of lecanemab are unknown in asymptomatic patients in whom only Aβ pathology has been confirmed as well as in patients with moderate or severe AD-D. Therefore, lecanemab treatment should not be initiated in these patients.

The appropriateness of the decision above and details of the indication and related cautionary statements will be finalized taking into account the comments from the Expert Discussion.

7.R.6 Dosage and administration

7.R.6.1 Recommended dosage regimen

The applicant's explanation about the dosage regimen of lecanemab:

Study 201 Core investigated lecanemab regimens of 2.5 mg/kg biweekly, 5 mg/kg monthly, 5 mg/kg biweekly, 10 mg/kg monthly, and 10 mg/kg biweekly. Among them, the least degree of worsening in the clinical assessment scale compared with placebo was observed in the 10 mg/kg biweekly group. During Study 201 Core, allocation of ApoE ε4 carriers to 10 mg/kg biweekly was discontinued in accordance with the recommendation made by the Data and Safety Monitoring Board and EMA [see Section "7.2 Global phase II study"]. However, this action was based on limited safety information at the beginning of Study 201 Core, and safety information on other anti-Aβ antibodies, not lecanemab. Additionally, the results of Study 201 Core indicated no clinically unacceptable risks for ApoE ε4 carriers in the 10 mg/kg biweekly group. Given that lecanemab can be administered without up-titration from low doses in patients including ApoE ε4 carriers as long as appropriate monitoring is implemented, the 10 mg/kg biweekly regimen was selected as the dose for Study 301. In Study 301 Core, the efficacy of lecanemab was demonstrated not only for the primary endpoint of CDR-SB, but also for secondary endpoints and changes in related biomarkers [see Section "7.R.3 Efficacy"]. In view of the safety data obtained from the clinical studies, the risk of the 10 mg/kg biweekly regimen was considered acceptable [see Section "7.R.4 Safety"].

Taken together, the dosage regimen of Study 301 Core was considered to be appropriate as the proposed dosage regimen of lecanemab. Therefore, the proposed dosage regimen of lecanemab was selected as follows: "The usual dosage is 10 mg/kg of lecanemab (genetical recombination) administered as an intravenous infusion over approximately 1 hour, once every 2 weeks."

PMDA's view:

On the basis of the efficacy and safety observed in Study 301, lecanemab 10 mg/kg can be administered biweekly regardless of the ApoE ε4 carrier status if cautionary advice is given to ensure that safety measures equivalent to those implemented in Study 301 against predictable risks including ARIA are implemented, and thus the proposed dosage regimen is appropriate.

7.R.6.2 Decision on continuation or discontinuation of treatment

PMDA asked the applicant to explain whether continuous treatment with lecanemab is expected to slow the progression of symptoms in patients in whom the severity of AD-D worsened to moderate or severe during the course of treatment with lecanemab.

The applicant's explanation:

Table 84 shows the baseline demographic and disease-related characteristics of subjects who progressed to moderate or severe[58)] AD-D during the study period of Study 301 Core ("progression group") and those who did not ("non-progression group"), and Table 85 shows the change in CDR-SB from the time of progression to moderate or to severe AD-D. Among subjects treated with lecanemab, the proportion of subjects in the progression group was higher than that in the non-progression group at baseline based on the following measures: global CDR score of 1 (67.6% [progression] and 17.2% [non-progression]), AD clinical diagnosis of mild AD-D (73.5% [progression] and 37.1% [non-progression]), use of symptomatic AD medications (67.6% [progression] and 51.4% [non-progression]), time from onset of AD (5.16 years [progression] and 4.09 years [non-progression]), and mean CDR-SB (4.87 [progression] and 3.10 [non-progression]), indicating that the disease had tended to be relatively progressed before the start of treatment with lecanemab. The results of change in CDR-SB from the time of progression to moderate or to severe AD-D (Table 85) do not suggest a trend toward worsening of clinical symptoms in the progression group receiving lecanemab compared with those in the progression group receiving placebo. However, given that a small sample size and a subgroup analysis based on the outcome after treatment can introduce bias, strict evaluation of the efficacy of lecanemab is difficult using these results.

Table 84. Baseline demographic and disease-related characteristics of subjects in the progression and non-progression groups in Study 301 Core (FAS+)

	Progression group		Non-progression group	
	Placebo (N = 55)	Lecanemab (N = 34)	Placebo (N = 820)	Lecanemab (N = 825)
Age[a]	71.6 ± 7.75	71.0 ± 7.93	70.9 ± 7.80	71.5 ± 7.87
<65 years[b]	21.8 (12)	23.5 (8)	20.2 (166)	19.2 (158)
≥65 years and <75 years[b]	36.4 (20)	41.2 (14)	44.0 (361)	42.9 (354)
≥75 years[b]	41.8 (23)	35.3 (12)	35.7 (293)	37.9 (313)
ApoE ε4 carrier status				
Homozygous[b]	12.7 (7)	23.5 (8)	15.2 (125)	15.5 (128)
Heterozygous[b]	52.7 (29)	47.1 (16)	53.5 (439)	53.3 (440)
Non-carrier[b]	34.5 (19)	29.4 (10)	31.2 (256)	31.2 (257)
Use of concomitant symptomatic AD medication[b]	74.5 (41)	67.6 (23)	52.1 (427)	51.4 (424)
AD clinical diagnosis				
MCI due to AD[b]	23.6 (13)	26.5 (9)	64.8 (531)	62.9 (519)
Mild AD-D[b]	76.4 (42)	73.5 (25)	35.2 (289)	37.1 (306)
Years from onset of AD[a]	3.90 ± 1.995	5.16 ± 2.523	4.17 ± 2.560	4.09 ± 2.331
Global CDR score				
0[b]	0 (0)	0 (0)	0 (0)	0 (0)
0.5[b]	36.4 (20)	32.4 (11)	83.7 (686)	82.8 (683)
1[b]	63.6 (35)	67.6 (23)	16.3 (134)	17.2 (142)

a, Mean ± standard deviation
b, % (n)

[58)] Using the same definition for the calculation of time to worsening of CDR score, an exploratory endpoint, worsening to CDR score of ≥2 in 2 consecutive visits was expressed as progression to moderate AD-D; worsening to CDR score of 3 in 2 consecutive visits was expressed as progression to severe AD-D.

Table 85. Change over time in CDR-SB from the time of progression to moderate or to severe AD-D in the progression group in Study 301 Core (FAS+)

	Progression group	
	Placebo (N = 55)	Lecanemab (N = 34)
At the time of progression to moderate or to severe AD-D	N = 55 10.25 ± 1.404	N = 34 9.96 ± 1.208
Change from the time of progression at 3 months	N = 55 1.17 ± 1.476	N = 34 0.40 ± 1.205
Change from the time of progression at 6 months	N = 26 1.29 ± 2.001	N = 22 1.32 ± 1.803
Change from the time of progression at 12 months	N = 4 4.50 ± 1.000	N = 4 1.00 ± 3.559

Mean ± standard deviation

Table 86 shows the change from baseline in CDR-SB in the progression and non-progression groups in Study 301 Core. The change from baseline in CDR-SB in subjects treated with lecanemab is greater in the progression group than in the non-progression group, with the difference increasing over time. Of the 34 subjects in the progression group treated with lecanemab, the time when progression to moderate or to severe AD-D was confirmed was Month 3 (3 subjects), Month 6 (2 subjects), Month 9 (10 subjects), Month 12 (10 subjects), and Month 15 (9 subjects), indicating that number of subjects that progressed to moderate or to severe AD-D started to increase at Month 9, and were reported intermittently thereafter.

Table 86. Change from baseline in CDR-SB in the progression and non-progression groups in Study 301 Core (FAS+)

	Progression group		Non-progression group	
	Placebo (N = 55)	Lecanemab (N = 34)	Placebo (N = 820)	Lecanemab (N = 825)
Baseline	N = 55 4.88 ± 1.371	N = 34 4.87 ± 1.089	N = 820 3.11 ± 1.266	N = 825 3.10 ± 1.303
Change from baseline at Month 3	N = 51 1.14 ± 1.659	N = 33 1.59 ± 1.783	N = 798 0.30 ± 1.065	N = 791 0.22 ± 0.959
Change from baseline at Month 6	N = 52 2.38 ± 2.076	N = 32 2.50 ± 1.356	N = 776 0.48 ± 1.174	N = 766 0.33 ± 1.135
Change from baseline at Month 12	N = 50 4.54 ± 2.464	N = 32 4.78 ± 1.513	N = 729 0.85 ± 1.396	N = 733 0.56 ± 1.322
Change from baseline at Month 18	N = 46 6.82 ± 2.912	N = 30 6.42 ± 2.613	N = 711 1.17 ± 1.721	N = 684 0.89 ± 1.645

Mean ± standard deviation

In view of the above, the efficacy evaluation should be performed on a regular basis (e.g., first evaluation at around 1 year, and around every 6 months thereafter) after the start of treatment with lecanemab, and a cautionary statement should include consideration of the need to discontinue lecanemab when lecanemab treatment cannot be expected to demonstrate efficacy based on the clinical course of symptoms or other data, and when the severity of AD-D has progressed to moderate or to severe.

PMDA asked the applicant to explain whether the decision to continue treatment with lecanemab can be based on the amyloid accumulation in the brain as measured by amyloid PET.

The applicant considered that it is difficult to determine whether to continue treatment with lecanemab based on the assessment of amyloid accumulation in the brain by amyloid PET given the following factors:

- At the subject level, the correlation between the change from baseline in amyloid PET SUVr or the Centiloid scale and CDR-SB or other efficacy assessment scales was not demonstrated to be strong enough to predict the level of change in the scales in subjects in whom amyloid accumulation was reduced by lecanemab in either Study 201 Core or Study 301 Core [see Section "7.R.3.3 Biomarkers"].
- Among subjects treated with lecanemab in Study 301 Core, the change from baseline in the amyloid PET Centiloid scale was similar between the group of subjects that progressed to moderate or to severe AD-D and the non-progression group at all evaluation timepoints.
- In Study 301 Core, the results of the group in which amyloid PET status based on visual read did not convert to negative after treatment with lecanemab suggested slowing of decline in CDR-SB compared with placebo [see Section "7.R.3.3 Biomarkers"].

PMDA's view:

Lecanemab requires ongoing treatment every 2 weeks and safety monitoring including MRI on a regular basis during treatment. Given that this places a burden on patients, a cautionary statement should be provided advising that treatment should be evaluated on a regular basis to make sure that lecanemab treatment is not continued aimlessly. It is assumed from the mechanism of action that the efficacy of lecanemab can be obtained via the effect on brain Aβ level reduction, however, based on the applicant's explanation, it is difficult to use changes in brain Aβ level in individual patients to predict the efficacy of lecanemab and determine whether to continue treatment with lecanemab. Conversely, if clinical decline continues and progresses to moderate or severe AD-D, discontinuation of lecanemab should be considered because the efficacy of continuous treatment in patients whose condition has progressed in severity is not clear. During treatment with lecanemab, clinical symptoms should be assessed every 6 months and whether to continue treatment should be determined based on the assessment result given the following findings: in the clinical studies some patients who showed more rapid progression worsened as early as within 6 months; and the number of patients who progressed to a more advanced stage of severity started to increase at Month 9 and were reported intermittently thereafter.

On the basis of the above, PMDA concluded that the cautionary statement below should be included in the "Precautions concerning dosage and administration" section, and this will be finalized taking into account the comments from the Expert Discussion.

- During treatment with lecanemab, cognitive function testing and clinical symptom assessment by interview of patients, family members, and caregivers on subjective and objective symptoms should occur approximately every 6 months. If the course of clinical symptoms, severity of dementia, and other factors do not indicate that lecanemab shows its effectiveness, treatment with lecanemab should be discontinued.

7.R.7 Post-marketing investigations

The applicant's explanation about the post-marketing investigations:

The applicant has planned to conduct a specified use-results survey with a target sample size of 600 patients and a follow-up period of 32 weeks to investigate the data including occurrence of ARIA and injection reaction in clinical use. It is estimated that safety investigations are possible with a sample size of 600 patients because the incidence of cerebral hemorrhage, the lowest among ARIA events, was 0.6% in Study 301 Core. The survey is planned to gather various types of information, namely, the ApoE ε4 carrier status, which may have an effect on the occurrence of ARIA; detailed information on the concomitant use of antithrombotic drugs; brain MRI scan results before the start of treatment; and other information on patient characteristics important for the identification of the disease state of patients with AD. If a certain number of ARIA occurs in the survey, investigation of factors that may have an effect on the occurrence of ARIA will be made possible by combining the information collected.

In the ongoing Study 301 OLE, the applicant plans to conduct an analysis of data including efficacy endpoints when all subjects on treatment have completed Month 6 (planned schedule: database lock in June 2023 and analysis results obtained by December 2023).

PMDA's view:

Since serious adverse events associated with ARIA and injection reaction occurred in the clinical studies, it is appropriate to conduct a post-marketing surveillance for the purpose of investigating which patient characteristics may have an effect on or be related to the advisability of continuing treatment in clinical practice and to gather information on the occurrence of adverse events related to ARIA or injection reactions and analyze their risk factors. The objectives of the survey and the planned sample size should be reconsidered accordingly. The long-term safety and efficacy of lecanemab should be evaluated based on data that include the results of ongoing Study 301 OLE. The details of post-marketing surveillance, as well as 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 lecanemab has efficacy in slowing the progression of MCI due to AD and mild AD-D, and that lecanemab has acceptable safety in view of its benefits. Lecanemab is a monoclonal antibody targeting soluble AβPFs, and it is clinically meaningful to make this new therapy available in clinical settings as a new treatment option for the treatment of MCI due to AD and mild AD-D. PMDA considers that further discussions are necessary regarding efficacy, indication, dosage and administration, cautionary statements in the package insert, post-marketing investigations, and other issues related to lecanemab.

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

Review Report (2)

August 10, 2023

Product Submitted for Approval

Brand Name	Leqembi for Intravenous Infusion 200 mg Leqembi for Intravenous Infusion 500 mg
Non-proprietary Name	Lecanemab (Genetical Recombination)
Applicant	Eisai Co., Ltd.
Date of Application	January 16, 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).

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

1.1 Efficacy

While it is difficult to conclude that the results of Study 301 Core verified the disease-modifying effect of lecanemab, the expert advisors supported the PMDA's conclusion that data demonstrated clinically meaningful efficacy. The following comments were made by the expert advisors:

- In Study 301 Core, exploratory endpoints were analyzed. The rate of progression over time in clinical symptoms as measured by CDR-SB in the analysis with a linear mixed model showed a decreasing trend in the lecanemab group compared with placebo, and the time to worsening of global CDR score to the next stage was longer in the lecanemab group compared with placebo in the survival time analysis [see Section "7.R.3.1 Significance of results from clinical studies"]. Given that none of the approved symptomatic AD drugs can slow the rate of progression of clinical symptoms, it is meaningful to make lecanemab available in clinical settings as a new treatment option for early AD.
- It is important to provide information on the expected efficacy of lecanemab in an appropriate manner so that patients and their families do not overestimate the drug's efficacy.

- So far no biomarkers indicating the efficacy of lecanemab have been identified, and further investigation is desired.

1.2 Safety

(1) Treatment of patients who were not eligible to be enrolled in clinical studies due to safety concerns

At the Expert Discussion, the expert advisors supported the PMDA's conclusions shown below regarding the treatment with lecanemab in patients who were not eligible to be enrolled in Studies 201 Core and 301 Core:

- Lecanemab should be contraindicated in patients who present with vasogenic cerebral edema, ≥5 cerebral microhemorrhages, superficial siderosis, or >1 cm cerebral hemorrhages before the start of treatment with lecanemab.
- Treatment with lecanemab in patients with a history of transient ischemic attack, stroke, or seizures within 1 year may be acceptable based on the factors shown below, provided that monitoring and management of adverse events, treatment interruption, and other appropriate actions are taken. A cautionary statement to the effect that there is no treatment experience in these patient populations should be included in the package insert.
  - The tables below show the incidence of CNS hemorrhagic events including ARIA-H[51)] in Study 301 Core (Table 87) and Studies 201 OLE and 301 OLE (Table 88) with and without the history of transient ischemic attack/stroke. While the incidence of ARIA-H tends to be higher in subjects with a history of transient ischemic attack or stroke, no hemorrhagic events such as cerebral hemorrhage have been reported.
  - The tables below show the incidence of seizures[59)] in Study 301 Core (Table 89) and Studies 201 OLE and 301 OLE (Table 90) with and without a previous history of seizure. There is no trend towards an increase in the incidence in patients with a history of seizure.

Table 87. Incidence of CNS hemorrhagic events[51)] in Study 301 Core with and without a history of transient ischemic attack or stroke (Safety analysis set)

	With a history of transient ischemic attack/stroke		Without a history of transient ischemic attack/stroke	
	Placebo (N = 23)	Lecanemab (N = 20)	Placebo (N = 874)	Lecanemab (N = 878)
All CNS hemorrhagic events	13.0 (3)	30.0 (6)	9.6 (84)	17.5 (154)
Amyloid related imaging abnormality-microhaemorrhages and haemosiderin deposits	13.0 (3)	30.0 (6)	7.6 (66)	13.7 (120)
Superficial siderosis of central nervous system	0 (0)	10.0 (2)	2.5 (22)	5.5 (48)
Cerebral haemorrhage	0 (0)	0 (0)	0 (0)	0.6 (5)
Haemorrhage intracranial	0 (0)	0 (0)	0.1 (1)	0 (0)
Thalamus haemorrhage	0 (0)	0 (0)	0 (0)	0 (0)
Subarachnoid haemorrhage	0 (0)	0 (0)	0.1 (1)	0.2 (2)
Brain stem haemorrhage	0 (0)	0 (0)	0 (0)	0 (0)
Haemorrhagic cerebral infarction	0 (0)	0 (0)	0 (0)	0 (0)
Subdural haematoma	0 (0)	0 (0)	0.5 (4)	0.8 (7)
Subdural haemorrhage	0 (0)	0 (0)	0.1 (1)	0 (0)

% (n)

[59)] Standardised MedDRA Queries (SMQ) narrow "convulsions"

Table 88. Incidence of CNS hemorrhagic events[51)] in Studies 201 OLE and 301 OLE with and without a history of transient ischemic attack or stroke (Safety analysis set)

	201 OLE		301 OLE[a]			
	With a history of transient ischemic attack/stroke	Without a history of transient ischemic attack/stroke	With a history of transient ischemic attack/stroke		Without a history of transient ischemic attack/stroke	
	Lecanemab[b] (N = 5)	Lecanemab[b] (N = 175)	Placebo[c] (N = 19)	Lecanemab[c] (N = 14)	Placebo[c] (N = 695)	Lecanemab[c] (N = 657)
All CNS hemorrhagic events	40.0 (2)	17.1 (30)	21.1 (4)	28.6 (4)	15.7 (109)	9.7 (64)
Amyloid related imaging abnormality-microhaemorrhages and haemosiderin deposits	40.0 (2)	12.6 (22)	21.1 (4)	28.6 (4)	13.7 (95)	8.5 (56)
Superficial siderosis of central nervous system	20.0 (1)	4.0 (7)	5.3 (1)	0 (0)	5.6 (39)	1.1 (7)
Cerebral haemorrhage	0 (0)	0.6 (1)	10.5 (2)	0 (0)	0.1 (1)	0 (0)
Haemorrhage intracranial	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Thalamus haemorrhage	0 (0)	0 (0)	0 (0)	0 (0)	0.1 (1)	0 (0)
Subarachnoid haemorrhage	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Brain stem haemorrhage	0 (0)	0.6 (1)	0 (0)	0 (0)	0 (0)	0 (0)
Haemorrhagic cerebral infarction	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0.2 (1)
Subdural haematoma	0 (0)	0.6 (1)	0 (0)	0 (0)	0.3 (2)	0.2 (1)
Subdural haemorrhage	0 (0)	0.6 (1)	0 (0)	0 (0)	0 (0)	0 (0)

% (n)

a, Data with a cut-off date of December 1, 2022 were used.

b, Since there were only a few subjects who had been assigned to placebo in the Core study, data were analyzed without dividing into treatment groups of the Core study.

c, Indicates treatment in the Core study

Table 89. Incidence of seizures[59)] in Study 301 Core with and without a history of seizures (Safety analysis set)

	With a history of seizures		Without a history of seizures	
	Placebo (N = 3)	Lecanemab (N = 7)	Placebo (N = 894)	Lecanemab (N = 891)
All seizures	0 (0)	14.3 (1)	0.4 (4)	0.4 (4)
Acquired epileptic aphasia	0 (0)	0 (0)	0 (0)	0 (0)
Epilepsy	0 (0)	0 (0)	0 (0)	0 (0)
Focal dyscognitive seizures	0 (0)	0 (0)	0.2 (2)	0 (0)
Generalised tonic-clonic seizure	0 (0)	0 (0)	0 (0)	0.1 (1)
Partial seizures	0 (0)	0 (0)	0 (0)	0.1 (1)
Partial seizures with secondary generalisation	0 (0)	0 (0)	0 (0)	0.1 (1)
Petit mal epilepsy	0 (0)	0 (0)	0 (0)	0 (0)
Seizure	0 (0)	14.3 (1)	0.2 (2)	0.1 (1)

% (n)

Table 90. Incidence of seizures[59)] in Studies 201 OLE and 301 OLE with and without a history of seizures (Safety analysis set)

	201 OLE		301 OLE[a]			
	With a history of seizures	Without a history of seizures	With a history of seizures		Without a history of seizures	
	Lecanemab[b] (N = 4)	Lecanemab[b] (N = 176)	Placebo[c] (N = 3)	Lecanemab[c] (N = 6)	Placebo[c] (N = 711)	Lecanemab[c] (N = 665)
All seizures	0 (0)	2.3 (4)	33.3 (1)	0 (0)	1.0 (7)	1.1 (7)
Acquired epileptic aphasia	0 (0)	0.6 (1)	0 (0)	0 (0)	0 (0)	0 (0)
Epilepsy	0 (0)	0.6 (1)	0 (0)	0 (0)	0 (0)	0.5 (3)
Focal dyscognitive seizures	0 (0)	0.6 (1)	0 (0)	0 (0)	0.1 (1)	0 (0)
Generalised tonic-clonic seizure	0 (0)	0.6 (1)	0 (0)	0 (0)	0 (0)	0.2 (1)
Partial seizures	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0.2 (1)
Partial seizures with secondary generalisation	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Petit mal epilepsy	0 (0)	0 (0)	0 (0)	0 (0)	0.1 (1)	0 (0)
Seizure	0 (0)	0.6 (1)	33.3 (1)	0 (0)	0.7 (5)	0.3 (2)

% (n)
a, Data with a cut-off date of December 1, 2022 were used.
b, Since there were only a few subjects who had been assigned to placebo in the Core study, data were analyzed without dividing into treatment groups of the Core study.
c, Indicates treatment in the Core study

(2) Concomitant use of antithrombotic drugs (antiplatelet, anticoagulant, and thrombolytic drugs)

The comments below were made by the expert advisors. PMDA concluded that the concomitant use of lecanemab and antithrombotic drugs should be listed in the "precautions for co-administration," and this conclusion was supported by the expert advisors.

- It is not realistic to designate antithrombotic drugs as "contraindication for co-administration" considering the age and comorbidities of the intended patient population of lecanemab. In view of the results of the clinical studies, antithrombotic drugs should be listed in the "precautions for co-administration" to increase vigilance to ensure that lecanemab is used with caution.
- It is important to make sure that all healthcare professionals involved in the care of patients treated with lecanemab know that the patient is on lecanemab treatment, including those cases where the patient is receiving antithrombotic and lecanemab treatments in different healthcare facilities. Carrying a patient card would be a reasonable measure.

(3) Safety in ApoE ε4 carriers

The comments below were made by the expert advisors. PMDA concluded that lecanemab can be administered to homozygous *APOE4* carriers if strict risk management for ARIA is implemented, and this conclusion was supported by the expert advisors.

- The incidence of ARIA and the severity on imaging tend to increase with increase in the number of ApoE ε4 alleles; therefore, it is recommended to consider testing for the *APOE4* genotype prior to treatment with lecanemab.
- Although information on the risks associated with lecanemab should be provided, there is no need to require across-the-board testing for the *APOE4* genotype at present.

PMDA's conclusion based on the above discussion:

- On the basis of the findings identified after close examination of the incidence of ARIA in Study 301 as shown below, the frequency of MRI after the initiation of lecanemab should be as follows: in addition to 3 months and 6 months after the initiation of lecanemab treatment [see Section 7.R.4.1 (c) in Review Report (1)], an MRI scan should be performed at 2 months after the initiation of treatment with lecanemab.
  - Four patients who developed severe ARIA-E on MRI by Week 9 in Study 301 Core were all homozygous *APOE4* carriers.
  - Two of the 4 patients mentioned above presented with symptoms suggestive of ARIA at the time of MRI scan before the 5th dose of lecanemab. The remaining 2 patients were asymptomatic and had moderate ARIA on MRI before the 5th dose of lecanemab, but worsened to severe ARIA on MRI after interruption of treatment with lecanemab.
  - Safety in patients who continue to receive lecanemab after experiencing asymptomatic, moderate ARIA on MRI has not been established.
- Data on ARIA by ApoE ε4 carrier status should be gathered in the post-marketing setting, and necessary measures to ensure proper use of lecanemab should be considered based on the information obtained.
- The following issues should be included in the package insert or other materials to increase vigilance and information on the incidence of ARIA by ApoE ε4 carrier status should also be provided.

Warnings

- Prior to initiating treatment with lecanemab, explain to patients and their families and care givers the incidence of ARIA associated with lecanemab, risk of ARIA, testing necessary for risk management, and actions to be taken when ARIA occurs. Sufficient information on these matters also needs to be provided. Treatment should be started only after an explanation has been given and consent had been obtained. Instruct them to contact the primary care physician immediately if any abnormality is noted.

Important Precautions

- While the incidence of ARIA and severity of ARIA on MRI, and the incidence of symptomatic ARIA were higher in homozygous ApoE ε4 carriers than in heterozygous ApoE ε4 carriers and non-carrier, ARIA management including prespecified MRI scanning should be implemented regardless of the ApoE ε4 carrier status. Homozygous ApoE ε4 carriers account for approximately 15% of patients with AD.

Incidence of ARIA by *APOE4* genotype

	Non-carrier		Heterozygous carrier		Homozygous carrier	
	Placebo	Lecanemab	Placebo	Lecanemab	Placebo	Lecanemab
ARIA-E	0.3	5.4	1.9	10.9	3.8	32.6
ARIA-H	4.2	11.9	8.6	14.0	21.1	39.0

Incidence of adverse events in the clinical studies (%)

(4) Patients who died during the Study 301 OLE

The applicant reported the additional case of a subject who died after the data cut-off date for Study 301 OLE (April 15, 2022) after preparation of the Review Report (1) as shown in Table 91. The applicant explained that although a causal relationship between lecanemab and ARIA-E or ARIA-H could not be ruled out, the death

was deemed not related to lecanemab because the cause of death was atherosclerotic and hypertensive heart disease based on the autopsy result.

Table 91. Details of the subject who died after the data cut-off date for Study 301 OLE and was not included in Table 78 of Review Report (1) (Safety analysis set)

MCI /AD	Age (years)	Sex	Race	ApoE ε4 status	Treatment in Core study	Diagnosis	Onset[a] (days)	Confirmed concomitant antithrombotic	Clinical severity	Bleeding site
MCI	77	Female	White	Homozygous	Placebo	ARIA-E/ ARIA-H (cerebral microhomorrhage)	38	Heparin	Severe	—

a, After the start of OLE

The comments below were made by the expert advisors regarding the 3 deaths reported after the data cut-off date for Study 301 OLE (April 15, 2022) [Table 78 in Review Report (1) and Table 91 in Review Report (2)]. PMDA concluded that information on the cases where patients who developed cerebral hemorrhage or severe ARIA during treatment with lecanemab in Study 301 OLE and died later should be included in the package insert and other information materials.

- Although the applicant denied a causal relationship to the study drug, not only AD neuropathological changes, but also inflammatory response in the blood vessels have been confirmed in the patient who died after receiving a thrombolytic drug (female aged 63 years) presented in Table 78. There is a possibility that lecanemab may have induced cerebrovascular inflammation, causing the blood vessels to become fragile, resulting in cerebral hemorrhage triggered by thrombolytic therapy.
- In the patient presented in Table 91, multiple cerebral microhemorrhages were noted, and in addition to AD pathology, marked perivascular inflammatory findings were reported. These abnormal findings may be related to lecanemab.
- On the basis of the information presented, a causal relationship to lecanemab cannot be completely ruled out for any of the patients in Tables 78 and 91.
- Sufficient information should be provided regarding the cases of patients with cerebral hemorrhage and severe ARIA who died, and the information should be included in the package insert to increase vigilance.

(5) Risk of cerebral hemorrhage in patients with comorbid hypertension

The risk for cerebral hemorrhage in patients with comorbid hypertension was re-evaluated. In view of the finding below, PMDA concluded that a cautionary statement to the following effect should be described in the "Important precautions" section of the package insert: prior to treatment with lecanemab, patients should be examined for hypertension. Lecanemab should be administered with caution to patients with continuously elevated blood pressure, and appropriate blood pressure management should be performed during treatment.

- The incidence of significant symptomatic hemorrhagic events such as cerebral hemorrhage and subdural hematoma tended to be higher in patients with hypertension than in patients without hypertension although the number of patients experiencing the events was limited [Tables 74 and 75 in Review Report (1)].

(6) Infusion reaction

The expert advisors supported the following PMDA's conclusion:

Infusion reaction should be included in the "Clinically significant adverse reactions" while sufficient information including the details of events that occurred in the clinical studies and actions to be taken in response to the onset of infusion reaction should be provided using information materials. It is appropriate to include a cautionary statement in the package insert to the effect that administration of premedication such as an antihistamine should be considered prior to the next administration of lecanemab if patients experienced an infusion reaction at the initial administration.

1.3 Intended patient population and indication of lecanemab

The expert advisors supported the following PMDA's conclusion: before using lecanemab in clinical settings, information including the patient population in Study 301 Core and the expected efficacy of lecanemab treatment should be provided using the "Precautions concerning indication" section of the package insert or by other means.

The following comment was made by the expert advisor regarding the indication:

- Since the intended patient population of lecanemab are patients with MCI or mild dementia who have confirmed AD pathology findings, the statement on dementia in the indication section should be "mild dementia due to Alzheimer's disease" rather than "mild dementia of the Alzheimer type."

In light of the above discussions at the Expert Discussion, PMDA concluded that the indication of lecanemab should be as follows:

Indication

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

1.4 Dosage and administration

The expert advisors supported the following PMDA's conclusion: the dosage and administration of lecanemab should be the dosage regimen proposed by the applicant: "the usual dosage is 10 mg/kg of lecanemab (genetical recombination) administered as an intravenous infusion over approximately 1 hour, once every 2 weeks" and during treatment with lecanemab, clinical symptoms should be assessed approximately every 6 months to determine whether to continue treatment based on the assessment result. The following comments were made by the expert advisors regarding the indication:

- According to the statement, lecanemab treatment should be discontinued when patients progress to moderate or severe AD-D; however, given that the disease state of patients with early AD varies widely and lecanemab does not completely stop the progression of the disease, whether to continue treatment should be determined taking into consideration the condition of individual patients, the rate of progression of the disease, and other factors. For example, clinical symptoms of patients with mild AD-D close to moderate dementia in severity may progress to moderate AD-D relatively soon after the initiation of treatment with lecanemab. In such a case, instead of stopping treatment immediately after progression, the

physician should carefully determine whether to continue treatment by closely monitoring the course of clinical symptoms of the patient after the start of treatment.

- After treatment experience with lecanemab in clinical practice and after new data on biomarkers has been gathered, the criteria for deciding whether to continue treatment should be further discussed.
- There are only limited data on the efficacy of lecanemab when it is continued to be administered to patients with dementia which had progressed to a moderate or severe stage during treatment, and the information about the limitation should be provided to the healthcare professionals in an appropriate manner.

On the basis of the above discussions at the Expert Discussion, PMDA concluded that the following cautionary statement should be included in the "Precautions for dosage and administration" section of the package insert:

- During treatment with lecanemab, cognitive function testing and clinical symptom assessment by interview of patients, family members, and caregivers on subjective and objective symptoms should occur approximately every 6 months. If the course of clinical symptoms, severity of dementia, and other factors do not indicate that lecanemab shows its effectiveness, treatment with lecanemab should be discontinued. The efficacy of continuous treatment with lecanemab in patients in whom the severity of dementia has progressed to a moderate or severe stage during treatment with lecanemab has not been established.

1.5 Risk management plan (draft)

In view of the discussions presented in Section "7.R.7 Post-marketing investigations" in Review Report (1), comments from the expert advisors at the Expert Discussion, and discussion in Section 1.2 (3) in Review Report (2), PMDA concluded that the post-marketing surveillance should be conducted covering all patients who will be receiving lecanemab (all-case surveillance) until a certain level of safety of lecanemab is confirmed.

On the basis of the discussion above, PMDA has concluded that the risk management plan (draft) for lecanemab should include the safety and efficacy specifications presented in Table 92, and that the applicant should conduct the additional pharmacovigilance activities and risk minimization activities presented in Table 93 and specified use-results survey presented in Table 94.

Table 92. 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 (cerebral microhemorrhage, superficial siderosis, intracerebral hemorrhage) • Infusion reaction	None	• Use in patients with concomitant anticoagulant drugs • Long-term treatment
Efficacy specification		
None		

Table 93. 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 (long-term use) • Post-marketing clinical study[a]	• Disseminate data gathered during early post-marketing phase vigilance • Confirmation of proper use • Prepare and distribute information materials for healthcare professionals (proper use guide) • Prepare and distribute information materials for patients

a, The ongoing Study 301 OLE will be reclassified as a post-marketing clinical study after approval until lecanemab becomes available at each medical institution.

Table 94. Outline of specified use-results survey (draft)

Objective	To confirm safety and efficacy in clinical use
Survey method	Central registration system (all-case surveillance)
Population	Patients with early AD who receive lecanemab for the first time
Observation period	Standard observation period of 79 weeks. For patients who continue to receive lecanemab, a follow-up survey of up to 3 years should be performed whenever possible
Planned sample size	Number of patients who will register by the end of planned registration period (18-36 months[a])
Main survey items	ARIA-E, ARIA-H (cerebral microhemorrhage, superficial siderosis, cerebral hemorrhage), patient characteristics (e.g., sex, age, medical history, comorbidities, disease stage, ApoE ε4 carrier status), concomitant use of antithrombotic drugs, clinical symptom assessment of early AD, confirmation of Aβ pathology

a, Details should be re-examined as necessary based on the number of patients registered for the survey and other conditions.

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 5.3.5.1.4, CTD 5.3.5.1.5, and CTD 5.3.5.1.9) 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, it was confirmed that the study was generally conducted in compliance with GCP, and PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted. The inspection revealed the following finding at some study centers used by the applicant. Although the issues had no significant impact on the overall assessment of the studies, the heads of the medical institutions concerned were notified of these issues as the findings requiring improvement:

Finding requiring corrective action:

CTD 5.3.5.1.4 and 5.3.5.1.5

Study centers

• Insufficient description in the partial outsourcing contract for the trial-related duties

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 approval conditions shown below. Since the product is a drug with a new active ingredient, the re-examination period is 8 years, and 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 dosage is 10 mg/kg of lecanemab (genetical recombination) administered as an intravenous infusion over approximately 1 hour, once every 2 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 collect information on patient characteristics until data from a specified number of patients are accrued. Furthermore, the applicant should collect data on the safety and efficacy of the product early and take necessary action to ensure the proper use of the product.

Appendix

List of Abbreviations

Aβ	Amyloid β
AD	Alzheimer's disease
ADA	Anti-drug antibodies
ADAS-Cog14	Alzheimer's Disease Assessment Scale-Cognitive subscale with 14 tasks
ADCOMS	Alzheimer's Disease Composite Score
ADCP	Antibody dependent cellular phagocytosis
ADCS	Alzheimer's Disease Cooperative Study
ADCS MCI-ADL	Alzheimer's Disease Cooperative Study-Activities of Daily Living Scale for Mild Cognitive Impairment
AD-D	Alzheimer's disease dementia
ADNI	Alzheimer's Disease Neuroimaging Initiative
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
AUC	Area under the concentration-time curve
AUC_{0-x}	AUC from time zero to fixed time-point x
AUC_{0-inf}	AUC from time zero to infinity
$AUC_{0-\tau}$	AUC for a dosing interval
BA	Bioavailability
BLAST	Basic local alignment search tool
BLI	Biolayer interferometry
$C_{0.083h}$	Concentration at 5 minutes after the dose
$C_{3.083h}$	Concentration at 3 hours and 5 minutes after the dose
CDR	Clinical Dementia Rating
CDR-SB	Clinical Dementia Rating-Sum of Boxes
CE-SDS	Capillary electrophoresis-sodium dodecyl sulfate
ChE	Cholinesterase
CHO	Chinese hamster ovary
CI	Confidence interval
CL	Total clearance
C_{max}	Maximum observed concentration
COVID-19	Coronavirus Disease 2019
CQA	Critical quality attribute
CRP	C-reactive protein
CSF	Cerebrospinal fluid
$C_{ss, ave}$	Average steady-state concentration
C-SSRS	Columbia Suicide Severity Rating Scale
CTD	Common technical document
DNA	Deoxyribonucleic acid
Donepezil	Donepezil hydrochloride
Early AD	Mild cognitive impairment and mild dementia due to Alzheimer's disease (MCI due to AD and mild AD-D)

EC_{50}	50% effective concentration
ECL	Electrochemiluminescence
ECLIA	Electrochemiluminescence immunoassay
ED_{90}	The dose regimen with at least 90% of the maximum effective dose treatment effect
EEPCB	Extend end of production cell bank
[redacted]	[redacted]
ELISA	Enzyme-linked immunosorbent assay
EMA	European Medicines Agency
Fab	Antigen-binding fragment
FAS	Full analysis set
FcR	Fc receptor
FcRn	Neonatal Fc receptor
FcγR	Fcγ receptor
FDA	United States Food and Drug Administration
Galantamine	Galantamine hydrobromide
GDS	Geriatric depression scale
HCP	Host cell protein
H/D	Hydrogen/deuterium
HLA	Human leukocyte antigen
HLT	High level terms
IC_{50}	Concentration causing a 50% reduction
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)
[redacted]C	[redacted] chromatography
IgG	Immunoglobulin G
IL-2	Interleukin-2
IP	Immunopurification
k_a	Association rate constant
k_d	Dissociation rate constant
K_D	Equilibrium constant
LC-MS	Liquid chromatography mass spectrometry
LC-MS/MS	Liquid chromatography coupled with tandem mass spectrometry
[redacted]	[redacted]
LDH	Lactate dehydrogenase
Lecanemab	Lecanemab (genetical recombination)
Leqembi	Leqembi for Intravenous Infusion
LTP	Long-term potentiation
MCB	Master cell bank
MCI	Mild cognitive impairment
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
MS	Mass spectrometry
NCI-CTCAE	National Cancer Institute-common terminology criteria for adverse events
NfL	Neurofilament light chain
NIA-AA	National Institute of Aging-Alzheimer's Association Workgroup
NMDA	*N*-methyl-D-aspartate
OLE	Open-label extension
PBMC	Peripheral blood mononuclear cell
PBS	Phosphate-buffered saline
PD	Pharmacodynamics
PET	Positron emission tomography
PF	Protofibril
PK	Pharmacokinetics
PMDA	Pharmaceuticals and Medical Devices Agency
PPK	Population pharmacokinetics
PT	Preferred term
p-tau	Phosphorylated tau
RAR	Response-adaptive randomization
RH	Relative humidity
SAE	Serious adverse event
SEC	Size exclusion liquid chromatography
SOC	System organ class
SPR	Surface plasmon resonance
SUVr	Standard uptake value ratio
$t_{1/2}$	Terminal elimination phase half-life
Tg	Transgenic
THBS1	Thrombospondin 1
t_{max}	Time at which the highest drug concentration occurs
t-tau	Total tau
V_c	Central volume of distribution
V_p	Peripheral volume of distribution
V_{ss}	Volume of distribution at steady state
WCB	Working cell bank
WMS-IV LM II	Wechsler Memory Scale-IV Logical Memory (subscale) II