Report on the Deliberation Results

December 6, 2024
Pharmaceutical Evaluation Division, Pharmaceutical Safety Bureau
Ministry of Health, Labour and Welfare

Brand Name	Tauvid Injection
Non-proprietary Name	Flortaucipir (^{18}F)
Applicant	PDRadiopharma Inc.
Date of Application	April 9, 2024

Results of Deliberation

In its meeting held on December 2, 2024, the First Committee on New Drugs concluded that the product may be approved and that this result should be presented to the Pharmaceutical Affairs Council.

The product is not classified as a biological product or a specified biological product. The re-examination period is 8 years. Neither the drug product nor its drug substance is classified as a poisonous drug or a powerful drug.

Approval Conditions

1. The applicant is required to develop and appropriately implement a risk management plan.
2. Taking into account the product's characteristics as radiopharmaceutical, the applicant is required to appropriately set manufacturing and quality control testing items for product release decision, and take proper post-marketing measures to ensure appropriate distribution control based on the testing results.

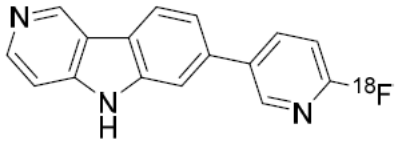
Review Report

November 13, 2024
Pharmaceuticals and Medical Devices Agency

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

Brand Name	Tauvid Injection
Non-proprietary Name	Flortaucipir (^{18}F)
Applicant	PDRadiopharma Inc.
Date of Application	April 9, 2024
Dosage Form/Strength	Injection: Each vial (1-9 mL) contains 370 MBq of flortaucipir (^{18}F) at the date and time of calibration (the date and time of administration to the patient)
Application Classification	Prescription drug, (1) Drug with a new active ingredient

Chemical Structure



Molecular formula: $C_{16}H_{10}[^{18}F]N_3$
Molecular weight: 262.27
Chemical name: 7-(6-[^{18}F]fluoropyridin-3-yl)-5*H*-pyrido[4,3-*b*]indole

Items Warranting Special Mention

Expedited review (PSB/PED Notification No. 0926-2 dated September 26, 2024)

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 aiding in the appropriate administration of donanemab (genetical recombination) in patients with mild cognitive impairment or 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 below, with the following conditions.

Indication

Aiding in appropriate administration of donanemab (genetical recombination) in patients with mild cognitive impairment or mild dementia due to Alzheimer's disease

Dosage and Administration

The dose is 370 MBq of flortaucipir (^{18}F) administered intravenously. Image acquisition should start approximately 80 minutes after administration. The imaging duration is 20 minutes.

Approval Conditions

1. The applicant is required to develop and appropriately implement a risk management plan.
2. Taking into account the product's characteristics as radiopharmaceutical, the applicant is required to appropriately set manufacturing and quality control testing items for product release decision, and take proper post-marketing measures to ensure appropriate distribution control based on the testing results.

Attachment

Review Report (1)

October 8, 2024

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

Product Submitted for Approval

Brand Name	Tauvid Injection
Non-proprietary Name	Flortaucipir (^{18}F)
Applicant	PDRadiopharma Inc.
Date of Application	April 9, 2024
Dosage Form/Strength	Injection: Each vial (1-9 mL) contains 370 MBq of flortaucipir (^{18}F) at the date and time of calibration (the date and time of administration to the patient).
Proposed Indication	Evaluation of the density and distribution of neurofibrillary tangles in the brain in patients with cognitive impairment who are suspected of having Alzheimer's disease

Proposed Dosage and Administration

The dose is 370 MBq of flortaucipir (^{18}F) administered intravenously. Image acquisition should start approximately 80 minutes after administration. The imaging duration is 20 minutes.

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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 characterized by clinical manifestations such as decreased cognitive function. Aggregates of amyloid β (Aβ) accumulate outside neuronal cells and form amyloid plaques, which is followed by the aggregation and accumulation of phosphorylated tau inside neuronal cells that form neurofibrillary tangles (NFTs). This causes neuronal cell death, inducing clinical symptoms such as a decline in cognitive function (*Alzheimers Dement*. 2011;7:280-292).

Flortaucipir (^{18}F) is radioactive fluorine (^{18}F)-labeled flortaucipir, a low-molecular compound that binds to tau. It was developed as a radioactive diagnostic agent for positron emission tomography (PET) scans by Siemens Molecular Imaging-Biomarker Research in the United States (US). The clinical development was initiated by Siemens in 2012. Flortaucipir (^{18}F) was approved for the indication of evaluation of the distribution of NFTs in the brain of patients with cognitive impairment suspected of having AD in the US in May 2020 and in Europe in August 2024.

Recently, the applicant filed an application for marketing approval of flortaucipir (^{18}F) with the proposed indication of "evaluation of the density and distribution of neurofibrillary tangles in the brain in patients with cognitive impairment who are suspected of having Alzheimer's disease," based on data including the results of a global phase III study of donanemab (genetical recombination) in patients with early AD with mild to severe brain tau accumulation detected by PET using flortaucipir (^{18}F) (AACI study) [see Section 7.1.2].

2. Quality and Outline of the Review Conducted by PMDA

2.1 Drug substance

Since the amount of flortaucipir (^{18}F) manufactured is very small and the physical half-life of ^{18}F is as short as approximately 110 minutes, flortaucipir (^{18}F) is formulated without being isolated, controlled, or stored as the drug substance in the manufacturing process. Therefore, specifications for AV-1622, a critical intermediate for ensuring the quality of the drug substance, have been set, and its stability data have been submitted.

2.1.1 Characterization

The general properties of the drug substance, including physical half-life, decay mode, released gamma-ray energy, partition coefficient, and specific radioactivity, have been determined. In addition, dissociation constant (K_d), partition coefficient, and solubility have also been determined using flortaucipir (^{19}F) having a chemical structure in which ^{18}F of flortaucipir (^{18}F) was replaced with the stable isotope ^{19}F.

The chemical structure of the drug substance has been elucidated by structure determination of flortaucipir (^{19}F) (elemental analysis, infrared absorption spectroscopy [IR], nuclear magnetic resonance spectroscopy [NMR] [^{1}H-NMR and ^{13}C-NMR], 2-dimensional NMR [^{1}H-^{1}H COSY-NMR, HSQC-NMR, and HMBC-NMR], mass spectrometry [MS], and X-ray crystallography). The chemical structure of AV-1622 has been elucidated by elemental analysis, IR, ultraviolet-visible spectrophotometry (UV/VIS), NMR (^{1}H-NMR and ^{13}C-NMR), 2-dimensional NMR (HSQC-NMR and HMBC-NMR), MS, and X-ray crystallography.

2.1.2 Manufacturing process

AV-1622 is manufactured through a process comprised of [redacted] steps using [redacted] as the starting material. Flortaucipir (^{18}F) is then manufactured through a process comprised of [redacted] steps including radioactive labeling, [redacted], and [redacted].

Critical steps are the manufacture of [redacted] and the manufacture of [redacted]. In-process control parameters and control values have been set for all [redacted] steps for the manufacture of AV-1622 from the starting material ([redacted]).

2.1.3 Control of AV-1622

The proposed specifications for AV-1622 consist of content, description (appearance), identification (IR), purity (related substance [high performance liquid chromatography (HPLC)], inorganic impurities [residue on ignition test], and residual solvents [gas chromatography (GC)]), water content, bacterial endotoxins (chromogenic method), and assay (HPLC).

2.1.4 Stability of AV-1622

Table 1 shows the main stability studies performed on AV-1622. The results of the long-term testing and intermediate testing demonstrated the stability of AV-1622, whereas the accelerated testing showed trends towards a decrease in the content of AV-1622, a decrease in purity, and increases in related substances at 6 months for all 3 batches. Photostability testing showed that AV-1622 was photostable.

Table 1. Main stability studies of AV-1622

Study	Primary batch	Temperature	Humidity	Storage condition	Storage period
Long-term	3 commercial-scale batches	25°C	60% RH	Amber borosilicate glass vial + polypropylene cap with PTFE/silicone septum	42 months
Intermediate		30°C	65% RH		12 months
Accelerated		40°C	75% RH		6 months

In view of the above, a shelf life of 42 months was proposed for AV-1622 when placed in an amber borosilicate glass vial sealed with a polypropylene cap with a polytetrafluoroethylene (PTFE)/silicone septum at room temperature.

2.2 Drug product

2.2.1 Description and composition of the drug product and formulation development

The drug product is a solution for injection supplied in vials each filled with 1 to 9 mL (labeled volume) of bulk solution containing of 800 or 1900 MBq/mL (at the end of synthesis [EOS]) of flortaucipir (^{18}F), and contains 370 MBq of flortaucipir (^{18}F) per vial at the date and time of calibration. Excipients contained in the drug product are anhydrous ethanol, isotonic sodium chloride solution, anhydrous disodium hydrogen phosphate, and dilute hydrochloric acid.

2.2.2 Manufacturing process

The drug product is manufactured through a process comprised of the following steps: [redacted], [redacted], [redacted], filling/stoppering, crimping/appearance inspection/labeling, labeling/packaging, and testing.

Critical steps are [redacted], [redacted], and filling/stoppering. In-process control parameters and control values have been set for the critical steps, and crimping/appearance inspection/labeling and labeling/packaging.

2.2.3 Control of the drug product

The proposed specifications for the drug product consist of strength, description (appearance), identification (gamma-ray measurement and HPLC), pH, purity (radiochemical impurities [HPLC], chemical impurities [HPLC], residual solvents [GC], Kryptofix 222 [chromogenic method], radionuclides [gamma-ray measurement]), insoluble foreign matter, bacterial endotoxins[1)] [redacted], filter integrity test, sterility, and assay (radioactivity [gamma-ray measurement], [redacted], and ethanol [GC]).

2.2.4 Stability of the drug product

Table 2 shows the main stability study performed on the drug product. The results demonstrated the stability of the drug product. Bracketing was applied to the long-term testing. Accelerated testing and photostability testing were not performed on the drug product.

Table 2. Main stability studies of the drug product

Study	Radioactivity concentration (MBq/mL)	Labeled volume (mL)	Primary batch	Temperature	Humidity	Storage condition	Storage period
Long-term	800	1	3 commercial-scale batches	25°C	Ambient	Silica-coated borosilicate glass vial + Teflon-coated chlorinated butyl rubber stopper + aluminum cap	8 hours
		9					
	1900	1					10.5 hours
		9					

In view of the above, a shelf life of 7.75 hours (800 MBq/mL product) or 10.25 hours (1900 MBq/mL product) from the EOS was proposed for the drug product when placed in a silica-coated borosilicate glass vial sealed with a Teflon-coated chlorinated butyl rubber stopper and an aluminum cap at room temperature. The drug product is a radioactive substance and is therefore stored in a shielding container made of lead.

2.R Outline of the review conducted by PMDA

On the basis of the data submitted, PMDA has concluded that the quality of AV-1622 and the drug product is controlled in an appropriate manner. However, since the product is released before obtaining test results of part of the specifications with consideration for the extremely short half-life of ^{18}F [see Section 2.2.3], the applicant is required to implement distribution control based on "Concepts on the Control of Product Release from the Manufacturing Site Stipulated in Article 12 of the GMP Ordinance" (Administrative Notice dated July 15, 2014), and if the test results are not conforming, the applicant should take the necessary measures such as discontinuation of marketing.

1) Release control is based on "Concepts on the Control of Product Release from the Manufacturing Site Stipulated in Article 12 of the GMP Ordinance" (Administrative Notice dated July 15, 2014).

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

3.1 Primary pharmacodynamics

3.1.1 Binding activity to tau (CTD 4.2.1.1.2)

When flortaucipir (^{18}F) was added to tau isolated from the brain of AD patients, the K_d of flortaucipir (^{18}F) for tau was 0.57 nmol/L.

3.1.2 Binding specificity for tau in the brain sections of AD patients (CTD 4.2.1.1.3 [reference data]; CTD 4.3.4, *Alzheimer's Dement*, 2013;9:666-676 [reference data])

Autoradiography with flortaucipir (^{18}F) was performed on brain sections of AD patients. Signals of flortaucipir (^{18}F) were detected in the tau-positive,[2)] Aβ-positive[3)] brain section, but not in the tau-negative,[2)] Aβ-positive[3)] section.

3.1.3 Binding activity to tau in the brain of AD and non-AD patients (CTD 4.2.1.2.7 [reference data])

Autoradiography with flortaucipir (^{18}F) was performed on brain sections of both AD patients with brain tau accumulation and non-AD patients (patients with Pick's disease [PiD], progressive supranuclear palsy [PSP], or chronic traumatic encephalopathy [CTE] [Stage II-IV[4)]]). The proportion of brain sections with signals of flortaucipir (^{18}F) corresponding to the tau-positive area[5)] was 100% (13 of 13 sections) in AD patients, 0% (0 of 17 sections) in PiD patients, and 9% (2 of 23 sections) in PSP patients. Very weak signals were detected in the brain sections of Stage IV CTE patients, and no signals were detected in the brain sections of Stage II and III CTE patients.

3.2 Secondary pharmacodynamics

3.2.1 Effects on receptors, channels, transporters, and other molecules (CTD 4.2.1.3.1 [reference data])

The inhibitory effect of flortaucipir (^{19}F) on the binding of each of 72 target molecules (receptors, channels, transporters, etc.) and their corresponding radiolabeled ligands was investigated. The target molecules that showed ≥50% inhibition at 10 μmol/L of flortaucipir (^{19}F) were (a) norepinephrine transporter, (b) monoamine transporter, (c) polyamine site of glutamate receptor, (d) μ-opioid receptor, and (e) acetylcholinesterase, with a half maximal inhibitory concentration (IC_{50}) of (a) 2.2, (b) 0.4, (c) 2.7, (d) 1.0 to 10, and (e) 1.0 to 10 μmol/L, respectively.[6)]

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2) Tau was determined to be positive or negative based on immunohistochemical staining using anti-tau antibody (AT100).

3) Aβ was determined to be positive or negative based on immunohistochemical staining using anti-Aβ antibody.

4) The stage of CTE patients was classified as follows (*Brain*. 2013;136:43-64):
Stage II: NFTs are localized in the cerebral cortex (usually in the frontal lobe).
Stage III: NFTs are densely present over a wide area of the cortex and in the medial-temporal lobe, with a patchy, irregular distribution.
Stage IV: NFTs are densely present in the thalamus, hypothalamus, mammillary bodies, and brain stem, and moderately present in the basal ganglia (especially in the nucleus accumbens), and tau pathology is observed in the white matter tract.

5) Tau was determined to be positive or negative based on immunohistochemical staining using anti-tau antibody (AT8).

6) All IC_{50} values are ≥100-fold the maximum brain concentration (4 nmol/L, calculated by assuming that the maximum amount in the brain is 7.0% of the dose) following administration of flortaucipir (^{18}F) at the maximum clinical dose [see Footnote 9] in humans (with a blood volume of approximately 5.2 L; *Ann ICRP*. 2002;32:5-265, *Blood Volume Regulation, Encyclopedia of Neuroscience, Springer Berlin Heidelberg*. 2008;p430-435).

3.2.2 Binding activity to monoamine oxidase (MAO)-A (CTD 4.2.1.2.2 and CTD 4.2.1.2.6 [reference data], CTD 4.2.1.2.3 [reference data])

When flortaucipir (^{18}F) or a MAO-A ligand (fluoroethyl harmol [FEH] (^{18}F)) was added to tau isolated from the brain of AD patients and human recombinant MAO-A, the K_d of flortaucipir (^{18}F) for tau and MAO-A was 0.57 and 2.0 nmol/L, respectively. FEH (^{18}F) did not bind to tau, and the K_d of FEH (^{18}F) for MAO-A was 1.2 nmol/L.

Autoradiography with flortaucipir (^{18}F) was performed on brain sections of non-dementia patients in the presence of flortaucipir (^{19}F), FEH, or a MAO-A inhibitor (clorgyline) to investigate the binding activity of flortaucipir (^{18}F) to MAO-A. The binding activity of flortaucipir (^{18}F) to MAO-A decreased under all of these conditions.

After administration of a MAO-A/B inhibitor (pargyline) or normal saline to rats (Sprague-Dawley [SD]), a single intravenous dose of flortaucipir (^{18}F) or FEH (^{18}F) (200-400 μCi) was administered to the rats, and images were obtained by dynamic PET to calculate brain radioactivity concentrations. The brain radioactivity concentration in the flortaucipir (^{18}F) group peaked immediately after administration and thereafter decreased rapidly regardless of whether pargyline was administered or not. In the FEH (^{18}F) group, the brain radioactivity concentration in pargyline-treated rats decreased more rapidly than that in normal saline-treated rats.

3.2.3 Binding activity to MAO-B (CTD 4.2.1.2.4 and CTD 4.2.1.2.6 [reference data])

When a MAO-B ligand (safinamide) was added to human recombinant MAO-B in the presence of flortaucipir (^{19}F), FEH, a MAO-A inhibitor (clorgyline), or a MAO-B inhibitor (deprenyl), the IC_{50} of (a) flortaucipir (^{19}F), (b) FEH, (c) clorgyline, and (d) deprenyl was (a) 1.3, (b) >10, (c) 3.3, and (d) 0.066 μmol/L, respectively.

Autoradiography with flortaucipir (^{18}F) was performed on brain sections of non-dementia patients in the presence of flortaucipir (^{19}F), deprenyl, or safinamide. The binding of flortaucipir (^{18}F) to MAO-B decreased under all of these conditions.

3.3 Safety pharmacology

Table 3 shows the results of safety pharmacology studies.

Table 3. Summary of safety pharmacology studies

Organ system evaluated	Test system	Evaluation items/ methods, etc.	Dose[a]	Route of administration	Findings	CTD
Central nervous system	Rats (SD) (8 males/group)	Irwin method	0,[b] 50, 100, 200 μg/kg	i.v.	No effects	4.2.1.3.2
Cardiovascular system	HEK293 cells stably expressing hERG channel	hERG current	0.1, 0.3, 1 μmol/L	*In vitro*	Positive IC_{50}: 0.26 μmol/L[c]	4.2.1.3.5
	Dogs (Beagle) (3/sex/group)	Heart rate, ECG (telemetry)[d]	0,[b] 5, 15, 30, 60 μg/kg	i.v.	No effects	4.2.3.2.2
Respiratory system	Rats (SD) (8 males/group)	Respiration rate, tidal volume, minute volume	0,[b] 50, 100, 200 μg/kg	i.v.	No effects	4.2.1.3.4

a: Flortaucipir (^{19}F) was used.
b: 90% normal saline containing 9% ethanol and 1% Kolliphor HS 15
c: The IC_{50} value is approximately 17-fold the maximum blood concentration (15 nmol/L, calculated by assuming that administered flortaucipir (^{18}F) is distributed only in blood) following administration of flortaucipir (^{18}F) at the maximum clinical dose [see Footnote 9] in humans (with a blood volume of approximately 5.2 L; *Ann ICRP*. 2002;32:5-265, *Blood Volume Regulation*, *Encyclopedia of Neuroscience*, *Springer Berlin Heidelberg*. 2008;p430-435).
d: Only electrocardiography (ECG) was measured in the 60 μg/kg group.

3.R Outline of the review conducted by PMDA

3.R.1 Ability of PET using flortaucipir (^{18}F) to detect tau in the brain

The applicant's explanation:

In view of the following points, the high-order structure of tau in AD patients can be detected by PET using flortaucipir (^{18}F):

- Investigation using samples obtained from the brain of AD patients showed that flortaucipir (^{18}F) binds to tau [see Sections 3.1.1 and 3.1.2].
- In patients with brain tau accumulation, it is known that the isoform and shape of the accumulated tau in the brain vary depending on the disease background[7)] (*Neuropathol Appl Neurobiol*. 2015;41:3-23, *Alzheimer's Res Ther*. 2014;6:1-13, etc.). Flortaucipir (^{18}F) was found to bind to tau that has accumulated in the brain of AD patients, whereas it does not bind to tau that has accumulated in the brain sections of non-AD patients. These findings suggest that flortaucipir (^{18}F) selectively binds to the high-order structures of tau consisting of 3R and 4R isoforms that accumulate mainly as paired helical filaments (PHFs), which are observed in AD patients (*Biomolecules*. 2016;6:1-15) [see Section 3.1.3].
- While binding activity of flortaucipir (^{18}F) to MAO-A and MAO-B was suggested [see Sections 3.2.3 and 3.2.4], binding of flortaucipir (^{18}F) to MAO-A and MAO-B is unlikely to affect the ability of PET using flortaucipir (^{18}F) to detect tau in the brain, because the results[8)] of the standardized uptake value ratio (SUVr) calculated based on the results of PET using flortaucipir (^{18}F) in healthy adults and AD patients (*J Nucl Med*. 2017;58:1124-1131) are consistent with the known trends of brain tau accumulation in healthy adults and AD patients.

7) The main tau aggregates accumulated in tauopathies are as follows (*Biomolecules*. 2016;6:1-15, *Proc Natl Acad Sci US*A. 2015;112:E2039-E2047, etc.):
PSP: Single filament consisting of the 3R isoform alone.
PiD: Single filament consisting of the 4R isoform alone.
AD and CTE: PHF consisting of the 3R and 4R isoforms.

8) In AD patients, the SUVr in the middle frontal cortex, occipital cortex, inferior lateral temporal cortex, superior lateral temporal cortex, and occipital lobe, using the cerebellar cortex as the reference region, was >1 from immediately after administration of flortaucipir (^{18}F) and thereafter increased over time. In healthy adults, the ratio remained around 1 from immediately after administration.

In view of the results of studies on primary and secondary pharmacodynamics and the applicant's explanation, PMDA has concluded that PET using flortaucipir (^{18}F) is expected to provide information on the presence/absence of brain tau accumulation in AD patients.

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

Radioactivity in tissues was measured using a gamma counter, PET, or PET/computed tomography (CT). Unchanged flortaucipir (^{18}F) and its metabolites were measured using HPLC or liquid chromatography mass spectrometry (LC/MS) equipped with a radiation measuring instrument. Tissue radioactivity concentrations are expressed as the percentage of radioactivity in the tissue relative to the injected dose (corrected for attenuation) per unit tissue weight (%ID/g).

Unless otherwise specified, pharmacokinetic parameters are expressed as the mean.

4.1 Absorption (CTD 4.2.2.3.1 [reference data])

In mice (2 mice/time point) that received a single intravenous dose of 9.25 MBq of flortaucipir (^{18}F), the plasma radioactivity concentrations at 5, 15, and 30 minutes post-dose were 0.89, 0.68, and 0.64%ID/g, respectively.

4.2 Distribution

4.2.1 Tissue distribution (CTD 4.2.2.3.1 [reference data]. CTD 4.2.2.3.2 [reference data])

In mice (2 mice/time point) that received a single intravenous dose of 9.25 MBq of flortaucipir (^{18}F), radioactivity in excised organs or tissues was measured at 5, 15, and 30 minutes post-dose. Radioactivity concentrations were high in the brain, liver, and kidney, and the concentrations at 5, 15, and 30 minutes post-dose were 4.43%ID/g, 1.92%ID/g, and 0.62%ID/g, respectively, in the brain, 4.44%ID/g, 6.32%ID/g, and 5.99%ID/g, respectively, in the liver, and 14.99%ID/g, 9.91%ID/g, and 5.52%ID/g, respectively, in the kidney.

In rats (5 rats) that received a single intravenous dose of up to 14.8 MBq of flortaucipir (^{18}F), the brain radioactivity concentration peaked (0.5%ID/g) within 5 minutes post-dose, and decreased to <0.2%ID/g at 30 minutes post-dose.

In monkeys (2 monkeys) that received a single intravenous dose of approximately 200 MBq of flortaucipir (^{18}F), standardized uptake values (SUVs) were measured based on the PET images of the cerebral cortex, striatum, cerebellum, and white matter until 90 minutes post-dose. At all sites, the SUV peaked by 15 minutes post-dose and then decreased slowly. The maximum SUV tended to be lower in the white matter than in the cerebral cortex, striatum, and cerebellum.

In monkeys (3 monkeys) that received a single intravenous dose of approximately 200 MBq of flortaucipir (^{18}F), the whole-body PET/CT images at 5, 25, and 120 minutes post-dose showed that flortaucipir (^{18}F)-derived radioactive substances were mainly distributed in the lung and kidney at 5 minutes post-dose, and in the liver, bladder, and small intestine at 25 minutes post-dose.

4.2.2 Plasma protein binding (CTD 5.3.2.1.1)

When flortaucipir (^{19}F) (final concentration, 1 μmol/L) was added to (a) mouse, (b) rat, (c) dog, and (d) monkey plasma, the protein binding rates were (a) 88.8%, (b) 90.9%, (c) 80.8%, and (d) 90.1%, respectively.

4.3 Metabolism

4.3.1 *In vitro* metabolism (CTD 5.3.2.2.1)

When flortaucipir (^{19}F) (final concentration, 2 μmol/L) was added to cryopreserved mouse, rat, dog, and monkey hepatocytes, followed by incubation at 37°C for up to 168 hours, the main metabolites detected were the oxidized form and the glucuronide conjugate of flortaucipir (^{19}F).

4.3.2 *In vivo* metabolism

4.3.2.1 Metabolites in plasma and the brain (CTD 4.2.2.4.1)

In mice (2 mice/time point) that received a single intravenous dose of 29.6 MBq (800 μCi) of flortaucipir (^{18}F), unchanged flortaucipir (^{18}F) and 3 metabolites (Metabolites 1, 2, and 3 [all structurally unidentified]) were detected in plasma, and unchanged flortaucipir (^{18}F) and 1 metabolite (Metabolite 3) were detected in the brain at 2, 15, and 30 minutes post-dose. Table 4 shows the amount of radioactivity in unchanged flortaucipir (^{18}F) or its metabolites in plasma and the brain.

Table 4. Amount of radioactivity in unchanged flortaucipir (^{18}F) or its metabolites in plasma and the brain following single intravenous administration of flortaucipir (^{18}F)

	Time point (minutes)	Amount of radioactivity (nCi)[a]	
		Plasma	Brain
Unchanged flortaucipir (^{18}F)	2	57.6, 102	411, 431
	15	41.5, 50.2	86.1, 112
	30	33.4, 55.5	45.9, 59.7
Metabolite 1	2	0, 0	0, 0
	15	9.13, 9.48	0, 0
	30	0, 4.65	0, 0
Metabolite 2	2	0, 0	0, 0
	15	4.03, 9.88	0, 0
	30	10.1, 18.7	0, 0
Metabolite 3	2	4.56, 5.37	0, 7.01
	15	11.88, 17.99	0, 0
	30	6.82, 14.4	0, 0

a: Corrected for attenuation.

4.4 Excretion

The applicant's explanation:

Although no non-clinical pharmacokinetic studies investigating the excretion of flortaucipir (^{18}F) have been conducted, the results of tissue distribution studies in mice and monkeys [see Section 4.2.1] and clinical studies [see Section 6.2.2.1] suggest that flortaucipir (^{18}F) is mainly eliminated via biliary and renal excretion.

4.R Outline of the review conducted by PMDA

On the basis of the data submitted, PMDA has concluded that the non-clinical pharmacokinetics of flortaucipir (^{18}F) has been appropriately evaluated.

5. Toxicity and Outline of the Review Conducted by PMDA

The applicant submitted toxicity study data, in the form of results data from single-dose toxicity studies, repeated-dose toxicity studies, genotoxicity studies, and another toxicity study (a study on cytotoxicity). All of these studies were conducted using flortaucipir (^{19}F).

5.1 Single-dose toxicity

The acute toxicity of flortaucipir (^{18}F) was evaluated based on the results after the first dose in an extended single-dose toxicity study in rats and a 1-month repeated-dose toxicity study in dogs (Table 5). Since no deaths were observed in either study, the applicant determined the approximate lethal dose to be >300 μg/kg in rats and >60 μg/kg in dogs.

Table 5. Single- and repeated-dose toxicity studies (findings after the first dose)

Test system	Route of administration	Dose (μg/kg)	Main findings	Approximate lethal dose (μg/kg)	Attached data CTD
Male and female rats (SD)	i.v.	0,[a] 75, 150, 300	None	>300	4.2.3.1.1 (Reference data)
Male and female dogs (Beagle)	i.v.	0,[b] 5, 15, 30, 60[c]	None	>60	4.2.3.2.2

a: Normal saline containing 9% ethanol and 1% Solutol HS 15
b: Normal saline containing 9% ethanol and 1% Kolliphor HS 15
c: The data in the 60 μg/kg/day group were not used for toxicity evaluation following 1-month repeated intravenous administration because flortaucipir (^{19}F) was administered only on Day 1 and only ECG was examined in this group.

5.2 Repeated-dose toxicity

One-month repeated-dose toxicity studies were conducted in rats and dogs (Table 6). No toxicity findings related to administration of the test drug, including changes suggestive of local irritation at the administration site, were observed. In the 1-month repeated-dose toxicity studies in rats and dogs, the doses (100 and 30 μg/kg/day, respectively) at the no observed adverse effect level (NOAEL) were both approximately 50-fold the maximum clinical dose of flortaucipir (^{18}F) (20 μg)[9)] (calculated based on the body surface area value normalized assuming a human body weight of 60 kg).

Table 6. Repeated-dose toxicity studies

Test system	Route of administration	Administration period	Dose (μg/kg/day)	Main findings	NOAEL (μg/kg/day)	Attached data CTD
Male and female rats (SD)	i.v.	1 month (once daily)	0,[a] 20, 50, 100	None	100	4.2.3.2.1
Male and female dogs (Beagle)	i.v.	1 month (once daily)	0,[a] 5, 15, 30	30: Transient and mild increase in heart rate (female)	30[b]	4.2.3.2.2

a: Normal saline containing 9% ethanol and 1% Kolliphor HS 15
b: The finding observed in females in the 30 μg/kg/day group was a transient change. The applicant therefore considered that the toxicological significance of the finding was low.

9) Estimated as the total amount of flortaucipir (^{18}F) and flortaucipir (^{19}F) based on the maximum concentration of flortaucipir (^{19}F) and the maximum dosing volume of the preparation for administration.

5.3 Genotoxicity

Genotoxicity studies consisted of an *in vitro* bacterial reverse mutation assay, an *in vitro* chromosomal aberration assay in Chinese hamster ovary (CHO) cells, and an *in vivo* rat bone marrow micronucleus assay (Table 7). A significant increase in the number of revertant colonies was observed in the bacterial reverse mutation assay, and a significant increase in the number of cells with chromosomal aberrations was observed in the chromosomal aberration assay in CHO cells. The result of the rat bone marrow micronucleus assay was negative.

Table 7. Genotoxicity studies

Study		Test system	Metabolic activation (duration)	Concentration (μg/plate or μg/mL) or dose (μg/kg/day)	Result	Attached data CTD
In vitro	Bacterial reverse mutation assay	*Salmonella typhimurium*: TA98, TA100, TA1535, TA1537 *Escherichia coli*: WP2*uvrA*	S9[a]–/+	0,[b] 1.60, 5.00, 16.0, 50.0, 160, 500, 1600, 5000	Positive	4.2.3.3.1.1
	In vitro chromosomal aberration assay in mammalian cells	CHO cells	S9[a]– (3 hours)	0,[b] 5.34, 10.9, 22.2	Positive (≥10.9)	4.2.3.3.1.2
			S9[a]+ (3 hours)	0,[b] 10.9, 22.2, 31.8	Positive (≥22.2)	
			S9[a]– (20 hours)	0,[b] 2.62, 3.74, 5.34, 7.63	Positive (≥3.74)	
In vivo	Rodent micronucleus assay	Male and female rats (SD) Bone marrow		0,[c] 400, 800, 1600 Twice daily, 2 days, i.v.	Negative	4.2.3.3.2.1

a: Rat liver S9 fraction with metabolizing enzymes induced with Aroclor 1254
b: DMSO
c: Normal saline containing 9% ethanol and 1% Kolliphor HS 15

5.4 Other toxicity studies

5.4.1 Study on cytotoxicity (CTD 4.2.3.7.7.1 [reference data])

A normal human lung fibroblast cell line (medical research council cell strain 5 [MRC5]), mouse hepatocyte cell line (alpha mouse liver 12 [AML12]), human colon adenocarcinoma cell line (laboratory of surgery 174T [LS174T]), and human glioblastoma cell line (A172) were treated with flortaucipir (^{19}F) (100-10000 nmol/L) for 24 hours. No cytotoxicity was observed in any of these cell lines.

5.R Outline of the review conducted by PMDA

5.R.1 Genotoxicity of flortaucipir (^{18}F)

The applicant's explanation:

A significant increase in the number of revertant colonies was observed in the bacterial reverse mutation assay, and a significant increase in the number of cells with chromosomal aberrations was observed in the chromosomal aberration assay in CHO cells; however, in view of the following points, the genotoxicity of flortaucipir (^{18}F) is not expected to be a source of concern:

- Significant increase in the number of revertant colonies observed in the bacterial reverse mutation assay: Flortaucipir (^{18}F) is administered as a single dose, and the maximum clinical dose of flortaucipir (^{18}F) (20 μg)[9)] is well below the acceptable intake (120 μg/day) established according to the treatment duration, based on the threshold of toxicological concern (TTC) in "Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk (PSEHB/ELD Notification No. 1110-3 dated November 10, 2015)" (hereinafter referred to as the ICH M7 (R2)

guideline).

- Significant increase in the number of cells with chromosomal aberrations observed in the chromosomal aberration assay in CHO cells: Since the result of the rat bone marrow micronucleus assay was negative, also for administration at a dose (1600 μg/kg) that is far above the maximum clinical dose of flortaucipir (^{18}F) (20 μg),[9] flortaucipir (^{18}F) is unlikely to induce chromosomal aberrations in humans.

In addition, it is justified to use the maximum clinical dose of flortaucipir (^{18}F) (20 μg), which is below the TTC, as the basis for considering that the genotoxicity of flortaucipir (^{18}F) is not expected to be a source of concern, in view of the following points:

- Flortaucipir (^{18}F) and its putative metabolites in humans do not have chemical structures (aflatoxin-like structure, *N*-nitroso structure, alkylazoxy structure, etc.) for which an acceptable daily intake level should be established below that based on the TTC according to the ICH M7 (R2) guideline.
- In view of the following information on 9 compounds confirmed in a comprehensive database survey on the carcinogenicity information of compounds with a similar chemical structure to flortaucipir (^{18}F),[10] there is no need to establish an acceptable daily intake level below that based on the TTC for compounds with a similar chemical structure to flortaucipir (^{18}F):
  - Two compounds with a carboline structure like flortaucipir (^{18}F) (carbazoline and 2-amino-9*H*-pyrido[2,3-*b*]indole): Carbazoline is non-carcinogenic. Although 2-amino-9*H*-pyrido[2,3-*b*]indole is known to be carcinogenic, the acceptable daily intake was calculated to be 42.7 μg/day based on the median toxic dose (TD_{50}) (35.6 mg/kg/day) obtained from the carcinogenicity study results of 2-amino-9*H*-pyrido[2,3-*b*]indole in mice (*Carcinogenesis*. 1984;5:815-819).[11]
  - Seven heterocyclic amine compounds with lower similarity to flortaucipir (^{18}F) in chemical structure than the above 2 compounds (5-fluoroquinoline, 2-amino-3-methyl-9*H*-pyrido[2,3-*b*]indole, 1-methyl-5*H*-pyrido[4,3-*b*]indol-3-amine, 1,4-dimethyl-5*H*-pyrido[4,3-*b*]indol-3-amine, 7*H*-benzo[*c*]pyrido[2,3-*g*]carbazole, 13*H*-benzo[*g*]pyrido[3,2-*a*]carbazole, and fluvastatin): Data on carcinogenicity have been reported only for fluvastatin. The acceptable daily intake of fluvastatin was calculated to be 150 μg/day based on the TD_{50} (125 mg/kg/day) obtained from the carcinogenicity study results of fluvastatin (*Fundam Appl Toxicol*. 1994;23:9-20).[11] The TD_{50} of 5-fluoroquinoline has not been registered in the above database. The acceptable daily intake of a similar compound, quinoline, was calculated to be 5.7 μg/day based on the TD_{50} (4.75 mg/kg/day) obtained from the carcinogenicity study results of quinoline (*J Toxicol Sci*. 2018;43:113-127).[11]

Information regarding the significant increase in the number of revertant colonies observed in the bacterial reverse mutation assay and the significant increase in the number of cells with chromosomal aberrations observed in the chromosomal aberration assay in CHO cells will be provided in the package insert.

[10] Leadscope Advanced Software Version 2024-0.0-15 LSML 3.0.37 (The search was conducted using the Lhasa Carcinogenicity Database on June 14, 2024, or using the Carcinogenicity Potency Database and the Lhasa Carcinogenicity Database on September 1, 2024).
[11] Human body weight was assumed to be 60 kg.

PMDA has concluded that the applicant's evaluation of the genotoxicity of flortaucipir (^{18}F) and their responses are justified.

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

6.1 Summary of biopharmaceutic studies and associated analytical methods

Radioactivity in blood was measured using a gamma counter. Metabolites of flortaucipir (^{18}F) were measured using HPLC equipped with a radiation measuring instrument.

6.2 Clinical pharmacology

6.2.1 *In vitro* studies using human biomaterials

6.2.1.1 Plasma protein binding (CTD 5.3.2.1.1 [reference data])

When flortaucipir (^{19}F) (final concentration, 1 μmol/L) was added to (a) human plasma, (b) serum albumin solution (4%), (c) α-1 acid glycoprotein solutions (0.05% and 0.2%), and (d) hepatic microsomes, the protein binding rates were (a) 94.7%, (b) 88.8%, (c) 31.9% to 58.7%, and (d) 33.9%, respectively.

6.2.1.2 *In vitro* metabolism (CTD 5.3.2.2.1 [reference data])

When flortaucipir (^{19}F) (final concentration, 2 μmol/L) was added to cryopreserved human hepatocytes, followed by incubation at 37°C for up to 168 hours, the main metabolites detected were the oxidized form and the glucuronide conjugate of flortaucipir (^{19}F).

The applicant's explanation:

Following the addition of a non-specific cytochrome P450 (CYP) inhibitor (1-aminobenzotriazole) and an aldehyde oxidase inhibitor (hydralazine), the intrinsic clearance (CL_{int}) of flortaucipir (^{19}F) (final concentration, 2 μmol/L) decreased by 16% and 59%, respectively. Therefore, the main enzyme involved in the hepatic metabolism of flortaucipir (^{18}F) is aldehyde oxidase.

6.2.1.3 Enzyme inhibition (CTD 5.3.2.2.3 [reference data])

The inhibitory effect of flortaucipir (^{19}F) (0.08-80 μmol/L) on the metabolism of CYP isoforms (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A) was investigated using human hepatic microsomes and substrates of these isoforms. Flortaucipir (^{19}F) did not inhibit any of the CYP isoforms evaluated.

6.2.1.4 Enzyme induction

No studies on enzyme induction have been conducted.

The applicant's explanation:

The clinical dose of flortaucipir (^{18}F) is very small, and it is administered as a single dose and is rapidly eliminated from the plasma [see Section 6.2.2.2]. Therefore, flortaucipir (^{18}F) is unlikely to cause pharmacokinetic interactions mediated by enzyme induction.

6.2.1.5 Investigation of transporters (CTD 5.3.2.2.2 [reference data])

When flortaucipir (^{19}F) 5 μmol/L was added to Madin-Darby canine kidney (MDCK) cells engineered to express P-glycoprotein (P-gp), the apparent permeability coefficient (P_{app}) A→B was 15×10^{-6} cm/s, P_{app} B→A was 16×10^{-6} cm/s, and the efflux ratio (P_{app} B→A/P_{app} A→B) was 1.0.

The inhibitory effect of flortaucipir (^{19}F) (5 and 25 μmol) on the transport of P-gp substrates was investigated using MDCK cells engineered to express P-gp. Flortaucipir (^{19}F) did not inhibit the transport.

An *in vitro* study is ongoing to evaluate the potential of flortaucipir (^{18}F) as a substrate or inhibitor of transporters other than P-gp (breast cancer resistance protein [BCRP], organic anion transporters [OATs] OAT1 and OAT3, the organic cation transporter [OCT] OCT2, and multidrug and toxin extrusion [MATE] proteins MATE1 and MATE2-K).

6.2.2 Investigation in healthy subjects and patients

6.2.2.1 Foreign phase I study (Study A15; CTD 5.3.3.1.2; study period, January to June 2015)

A single intravenous dose of flortaucipir (^{18}F) 370 MBq was administered to 6 healthy non-Japanese subjects. Urine samples were collected from the subjects at 60, 150, and 360 minutes post-dose to obtain data on the urinary excretion of radioactivity following administration of flortaucipir (^{18}F). The obtained data were used to correct the data on radiation dose following administration of flortaucipir (^{18}F) obtained in another foreign phase I study (Study A01)[12)] and to estimate the systemic effective dose and the absorbed doses in each organ/tissue in Japanese and non-Japanese subjects.

The systemic effective dose was estimated to be 8.70 mSv/370 MBq using a standard adult male (body weight, 73.7 kg) model. The absorbed doses in each organ/tissue were similar in Japanese and non-Japanese subjects. Time-course changes in systemic PET images suggested that flortaucipir (^{18}F) is rapidly eliminated into the bile after administration.

6.2.2.2 Foreign phase II study (Study A10; CTD 5.3.3.2.2; study period, August 2015 to April 2017)

A single intravenous dose of flortaucipir (^{18}F) 240 MBq was administered to 20 non-Japanese subjects (10 healthy subjects and 10 AD patients). Table 8 shows the time-course changes in plasma radioactivity concentration, blood/plasma ratio of radioactivity, and percentage of unchanged flortaucipir (^{18}F) and its metabolites in plasma radioactivity (corrected for attenuation) up to 130 minutes post-dose.

[12)] Nine healthy subjects (3 Japanese and 6 non-Japanese subjects) received a single intravenous dose of flortaucipir (^{18}F) 370 MBq, and underwent systemic PET 10 times by 6 hours post-dose.

Table 8. Time-course changes in plasma radioactivity concentration, blood/plasma ratio of radioactivity, and percentage of the radioactivity of unchanged flortaucipir (^{18}F) and its metabolites in plasma radioactivity (corrected for attenuation)

Time point (minutes)	Plasma radioactivity concentration (MBq/g)	Blood/plasma ratio	Percentage in plasma radioactivity (%)	
			Unchanged flortaucipir (^{18}F)	Metabolites
5	0.0024 ± 0.00078	0.98 ± 0.057	86.4 ± 10.0	4.78 ± 6.18
10	0.0016 ± 0.00075	0.96 ± 0.062	75.0 ± 22.6	7.51 ± 8.32
15	0.0013 ± 0.00076	0.95 ± 0.062	69.7 ± 15.4	11.4 ± 7.99
20	0.0012 ± 0.00078	0.95 ± 0.062	58.9 ± 21.1	16.0 ± 9.49
40	0.0013 ± 0.00077	0.96 ± 0.074	42.5 ± 17.1	23.2 ± 9.72
60	0.0013 ± 0.00069	0.96 ± 0.085	37.4 ± 14.5	25.6 ± 8.60
80	0.0014 ± 0.00064	0.94 ± 0.098	34.0 ± 10.5	30.5 ± 6.87
105	0.0013 ± 0.00053	0.95 ± 0.099	28.2 ± 09.1	32.2 ± 6.77
130	0.0013 ± 0.00046	0.94 ± 0.095	22.6 ± 08.2	34.8 ± 7.38

Mean ± standard deviation

6.R Outline of the review conducted by PMDA

6.R.1 Transporter-mediated pharmacokinetic interactions

PMDA's view:

The final decision on the possibility of the occurrence of transporter-mediated pharmacokinetic interactions during the clinical use of flortaucipir (^{18}F) should be made based on the results of the ongoing non-clinical study [see Section 6.2.1.5] in the Review Report (2).

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

The applicant submitted main clinical efficacy and safety study data, in the form of results data from 2 studies shown in Table 9.

Table 9. Summary of main clinical studies

Data category	Region	Study identifier	Phase	Population	Number of enrolled subjects	Outline of dosage regimen	Main endpoints
Evaluation	Foreign	Study A16	III	Subjects aged ≥50 years and diagnosed with a life expectancy of ≤6 months	156 (Including 67 autopsy cases)	Flortaucipir (^{18}F) 370 MBq (10 mCi), single dose, i.v.	Efficacy Safety
Evaluation	Global	AACI study	III[a]	Early AD patients with mild to severe brain tau accumulation by PET using flortaucipir (^{18}F)	1736 (860 in the donanemab group and 876 in the placebo group)	Flortaucipir (^{18}F) 370 MBq (10 mCi), single dose, i.v.	Efficacy Safety

a: At the time of revision to Protocol (b) (February 17, 2021), the study phase was changed from phase II to confirmatory study of donanemab (phase III).

7.1 Phase III studies

7.1.1 Foreign phase III study (Study A16, CTD 5.3.5.2.4, October 2015 to June 2018)

An open-label, uncontrolled study was conducted at 28 foreign study sites to evaluate the diagnostic performance of PET using flortaucipir (^{18}F) in non-Japanese subjects aged ≥50 years and diagnosed with a life expectancy of ≤6 months by the investigator (target sample size, approximately 200 subjects[13)]).

The subjects received a single intravenous dose of flortaucipir (^{18}F) 370 MBq (10 mCi), and underwent brain PET for 20 minutes that started approximately 80 minutes post-dose.

13) For both the sensitivity and specificity of PET using flortaucipir (^{18}F), which were assessed as primary endpoints, the threshold and expected values were assumed to be 50% and 80%, respectively. For both sensitivity and specificity, the numbers of pathologically diagnosed positive and negative subjects necessary for the lower bound of the 95% CI to exceed the threshold value were both ≥14. Therefore, the target number of autopsy cases was set as 80 subjects, and the target sample size was set as 200 subjects.

All 156 enrolled subjects (103 subjects with dementia, 3 subjects with mild cognitive impairment [MCI], and 50 cognitively normal [CN] subjects) received flortaucipir (^{18}F) and were included in the safety analysis set. Of 67 subjects who died during the study period and were then autopsied,[14] a total of 64 subjects (49 subjects with dementia, 1 subject with MCI, and 14 CN subjects), excluding the first 3 autopsied subjects,[15] in whom the Alzheimer's disease neuropathologic change (ADNC) could be evaluated based on (a) Braak stage classification and (b) diagnostic criteria of the National Institute on Aging-Alzheimer's Association (NIA-AA), were included in the main efficacy analysis populations ((a) efficacy analysis set [EFF]1 and (b) EFF2, respectively). The study was discontinued in 86 subjects (48 subjects with dementia, 2 subjects with MCI, and 36 CN subjects), and the main reasons for discontinuation were survival for ≥9 months after PET in 39 subjects (36 subjects with dementia, 2 subjects with MCI, and 1 CN subject) and the sponsor's decision in 35 subjects (5 subjects with dementia, 0 subjects with MCI, and 30 CN subjects).

The primary efficacy endpoints[16] in the EFF1 and EFF2 groups were the sensitivity and specificity of antemortem PET image interpretation results using the NFT score and ADNC, respectively, as the standard of truth (SOT) at the time of autopsy. Table 10 shows the SOT assessment criteria for each analysis set.

Table 10. Assessment criteria for SOT

Population	SOT	Criteria
EFF1	Positive	NFT score at autopsy is B3.[a]
	Negative	NFT score at autopsy is B0 to B2.[a]
EFF2	Positive	The level of ADNC at autopsy is high.[b]
	Negative	ADNC at autopsy is absent, or the level is low or intermediate.[b]

a: Braak stages V and VI correspond to B3, and Braak stages I to IV correspond to B0 to B2 (*Acta Neuropathol*. 2006;112:389-404).
b: Assessed based on the NIA-AA diagnostic criteria (*Alzheimers Dement*. 2012;8:1-13).

PET images were read by 5 independent nuclear medicine specialists according to the criteria for interpretation shown in Table 11 under blinded conditions.

Table 11. Criteria for the interpretation of PET images

	Criteria
Positive	• An increase in the accumulation of flortaucipir (^{18}F) is observed in the neocortex of the posterolateral temporal lobe or occipital lobe in either hemisphere. • An increase in the accumulation of flortaucipir (^{18}F) is observed in the neocortex of the parietal region/precuneus, or the neocortex of the frontal lobe and the posterolateral temporal lobe, occipital lobe, parietal region, or occipital lobe in either hemisphere.
Negative	• No increase in the accumulation of flortaucipir (^{18}F) in the neocortex is observed. • An increase in the accumulation of flortaucipir (^{18}F) in the neocortex is observed, but only in the medial temporal lobe, anterolateral temporal lobe, and/or frontal lobe.

14) Of 70 subjects who died during the study period, 3 subjects were not autopsied.
15) The pathology results of the 3 subjects were not blinded, and the subsequent study procedures were modified based on these results. These subjects were not included in the main efficacy analysis populations.
16) In Protocol Version 1 (dated June 4, 2015), the primary endpoints were the sensitivity and specificity of flortaucipir (^{18}F) (EFF1) based on assessment by majority vote of 5 radiographic interpreters, with NFT scores at autopsy of B2 and B3 defined as SOT positive, and B0 and B1 defined as SOT negative, and the success criterion for the primary endpoints in Study A16 was the lower bound of the 95% confidence interval (CI) exceeding the threshold value of 55%. In reference to the clinical results of flortaucipir (^{18}F) (results of the explorative part of Study A05, etc.), the final primary endpoints were specified in Protocol Version 2 (dated December 18, 2017), with the success criterion in Study A16 defined as achieving the assessment criteria for both primary endpoints.

Table 12 shows the sensitivity and specificity of PET using flortaucipir (^{18}F), which were assessed as the primary endpoints, in the EFF1 and EFF2 groups. Both endpoints met the pre-defined success criterion (lower bound of the 95% confidence interval [CI] ≥50% for both sensitivity and specificity by ≥3 out of 5 interpreters).

Table 12. Sensitivity and specificity of PET using flortaucipir (^{18}F) (EFF1 and EFF2)

	EFF1 (N = 64)[a]		EFF2 (N = 64)[b]	
	Sensitivity (%)	Specificity (%)	Sensitivity (%)	Specificity (%)
Interpreter 1	97.4 [86.8, 99.5]	68.0 [48.4, 82.8]	97.4 [86.8, 99.5]	65.4 [46.2, 80.6]
Interpreter 2	92.3 [79.7, 97.3]	92.0 [75.0, 97.8]	94.7 [82.7, 98.5]	92.3 [75.9, 97.9]
Interpreter 3	92.3 [79.7, 97.3]	88.0 [70.0, 95.8]	94.7 [82.7, 98.5]	88.5 [71.0, 96.0]
Interpreter 4	92.3 [79.7, 97.3]	76.0 [56.6, 88.5]	94.7 [82.7, 98.5]	76.9 [57.9, 89.0]
Interpreter 5	100.0 [91.0, 100.0]	52.0 [33.5, 70.0]	100.0 [90.8, 100.0]	50.0 [32.1, 67.9]

Point estimate [95% CI]; 95% CI was calculated using the Wilson score method.
a: Consisting of 39 positive (NFT score, B3) and 25 negative (NFT score, B0-B2) subjects based on pathological diagnosis.
b: Consisting of 38 positive (ADNC, high level) and 26 negative (ADNC, absent or low or intermediate level) subjects based on pathological diagnosis.

The safety results are as follows: The incidence of adverse events within 48 hours after administration of flortaucipir (^{18}F) was 9.0% (14 of 156 subjects). The adverse events observed were agitation in 3 subjects, headache in 2 subjects, and acute kidney injury, cardiac failure congestive, diarrhoea, dizziness postural, fall, hypomagnesaemia, hypoxic-ischaemic encephalopathy, injection site bruising, mental disorder, myocardial infarction, myopathy, nausea, neoplasm malignant, procedural vomiting, restlessness, tremor, and vertigo in 1 subject each.

Death was observed in 2 subjects (acute kidney injury and neoplasm malignant), and a causal relationship to flortaucipir (^{18}F) was ruled out in both subjects. A serious adverse event other than death was observed in 1 subject (myocardial infarction), and its causal relationship to flortaucipir (^{18}F) was not ruled out.

7.1.2 Global phase III study (AACI study, CTD 5.3.5.1.1, June 2020 to April 2023)

A placebo-controlled, randomized, double-blind, comparative study was conducted at 277 Japanese and foreign study sites to confirm the superiority of the efficacy of donanemab over placebo in Japanese and non-Japanese early AD patients with mild to severe brain tau accumulation on PET using flortaucipir (^{18}F) (target sample size, approximately 1800 subjects [900 subjects each in the placebo and donanemab groups][17)]).

Table 13 shows the main changes to the study protocol of the AACI study.

[17)] In Protocol (c), the target sample size of subjects with mild to severe brain tau accumulation was set as approximately 1000 subjects, assuming the mean change in the iADRS score from baseline to Week 18 of treatment to be −10.06 in the placebo group and −6.86 in the donanemab group, with a common standard deviation of 11.06 and a dropout rate of 30%, based on the results of a foreign phase II study of donanemab (AACG study), to provide a >95% power to detect a statistically significant difference between the placebo and donanemab groups at a 2-sided significance level of 0.05 using the natural cubic spline model with 2 degrees of freedom (NCS2).

Table 13. Main changes to the study protocol of the AACI study

Protocol	Main changes
Version a (December 14, 2020)	The protocol was revised to administer 700 mg for the first 3 doses.
Version b (February 17, 2021)	• The study, initially planned as a phase II study, was switched to a confirmatory study (phase III) to evaluate the reproducibility of the results obtained in the AACG study.[a] • The primary endpoint was changed from CDR-SB to iADRS,[b] and the primary analysis model was changed from a MMRM to a Bayesian DPM. • In response to the results of the AACG study,[a)] the primary analysis population was changed from "the overall population or a subgroup of subjects with mild to moderate tau protein accumulation confirmed by PET" to "a subgroup of subjects with mild to moderate tau protein accumulation confirmed by PET." • In response to the changes including the primary endpoint, the target sample size of subjects with mild or moderate brain tau accumulation was changed to approximately 1000 subjects (approximately 1500 subjects as the overall population).
Version c (September 3, 2021)	The number of subjects to be enrolled in the double-blind period was increased by 300 because some of the results in the double-blind group would be submitted as safety data for the application of donanemab in the US.
Version d (October 5, 2021)	• A long-term treatment extension period was added. • The primary analysis population was revised again to "the overall population and a subgroup of subjects with mild to moderate tau protein accumulation confirmed by PET." • To identify the occurrence of amyloid-related imaging abnormalities (ARIAs) and their severity earlier, procedures to perform magnetic resonance imaging (MRI) scan 4 weeks after the first dose of the study drug and to confirm the results before the second dose were added.
Version e (November 10, 2022)	• The primary analysis model was changed from DPM to NCS2.

a: A foreign phase II study in early AD patients with mild or moderate brain tau accumulation to investigate the efficacy and safety of donanemab.
b: See Footnote 22.

The AACI study consisted of a lead-in period (as needed, before the complete screening period), a complete screening period (up to 7 weeks), a 76-week double-blind treatment period, a 78-week treatment extension period, and a follow-up period of up to 44 weeks. Subjects were randomized in a 1:1 ratio to the placebo or donanemab group, with stratification by study site and brain tau accumulation (mild or moderate vs. severe). During the double-blind treatment period, placebo or donanemab 1400 mg (700 mg[18)] for the first 3 doses) was intravenously administered once every 4 weeks. During the treatment extension period, all subjects transferred from the placebo group in the double-blind treatment period were assigned to the donanemab group. The subjects transferred from the donanemab group were assigned under double-blind conditions; those whose amyloid plaque reduction met the criteria for treatment completion[19)] on amyloid PET by Week 76 of the study treatment were assigned to the placebo group, while those who did not meet the criteria were assigned to the donanemab group. The dosage regimen of donanemab during the treatment extension period was 1400 mg (700 mg for the first 3 doses of subjects transferred from the placebo group in the double-blind treatment period), i.v., once every 4 weeks. However, for subjects who continued treatment with donanemab 700 mg[18)] in the double-blind treatment period, the dose could be increased to 1400 mg after Visit 25. If the subject's amyloid plaque reduction met the criterion for treatment completion[19)] based on amyloid PET using florbetapir (^{18}F) or florbetaben (^{18}F) at Weeks 24, 52, 76, 102, and 130 of the study treatment, the subject was switched to the placebo group under double-blind conditions (Figure 1). This section provides the results up to the end of the double-blind treatment period.

[18)] If ARIA occurred during the first 3 doses, the treatment could be continued at 700 mg thereafter based on the judgment of the investigator or subinvestigator.
[19)] Centiloid value <11 for any single scan, or ≥11 and <25 for two consecutive scans.

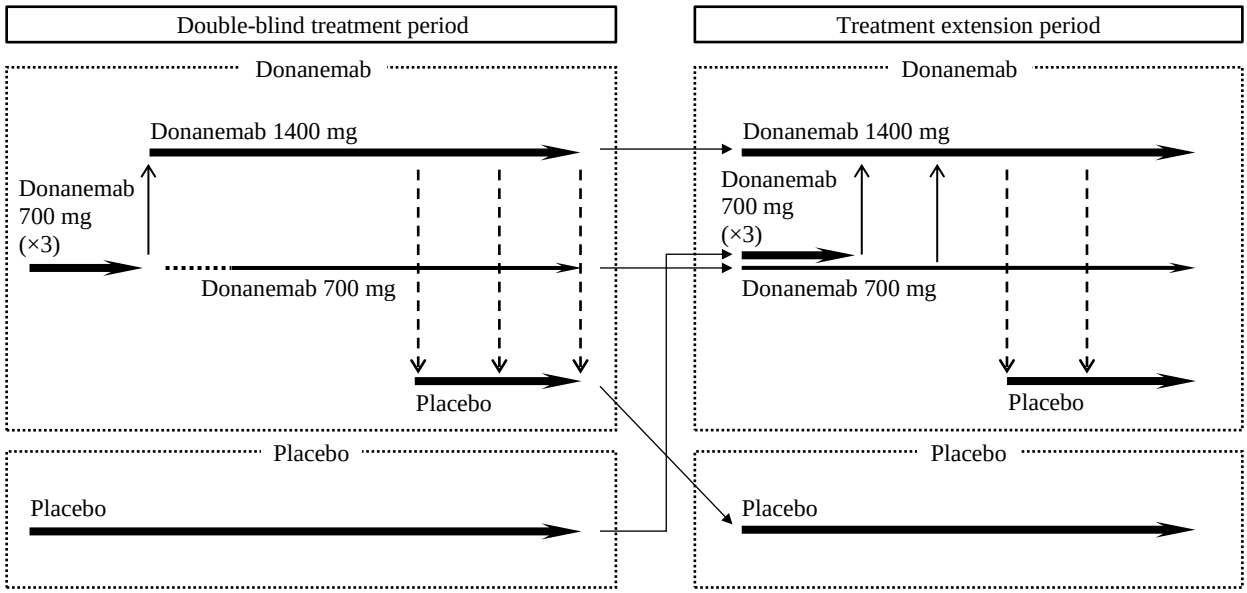

Figure 1. Outline of the AACI study design

At screening and at Weeks 76 and 154 of the study treatment, a single intravenous dose of flortaucipir (^{18}F) 370 MBq (10 mCi) was administered, followed by brain PET for 30 minutes that started approximately 75 minutes post-dose, to evaluate brain tau accumulation. PET images were evaluated by trained radiographic interpreters independent from the study sites.

Early AD patients aged 60 to 85 years who met the following main inclusion criteria were eligible for the study:

- Gradual progression of memory impairment over ≥6 months has been reported by the patient or his/her study partner.[20)]
- The result of amyloid PET using florbetapir (^{18}F) or florbetaben (^{18}F)[21)] is positive.
- The Mini-Mental State Examination (MMSE) score in the lead-in period or at screening is ≥20 and ≤28.
- The results of tau PET using flortaucipir (^{18}F) meet the following criteria:
  - Mild or moderate brain tau accumulation: A topographic deposition pattern on visual reading that corresponds to moderate AD (*JAMA Neurol*. 2020;77:829-839), with SUVr of ≥1.10 and ≤1.46, or a topographic deposition pattern on visual reading that corresponds to severe AD, with SUVr of ≤1.46.
  - Severe brain tau accumulation: A topographic deposition pattern on visual reading that corresponds to moderate or severe AD, with SUVr of >1.46.
- The MRI scan at screening does not show amyloid-related imaging abnormalities-edema/effusion (ARIA-E), ≥5 cerebral microhemorrhages, ≥2 superficial siderosis of central nervous system, any cerebral hemorrhage, or severe white matter lesions.

[20)] The study partner was defined as the person who had provided written informed consent for study participation, was available to commutate with the patient for ≥10 hours a week, and was able to accompany the patient to his/her study visits or contact the patient by telephone at specified times.
[21)] In Japan, only florbetapir (^{18}F) was used.

Overall population

Of 1736 randomized subjects (876 in the placebo group and 860 in the donanemab group; the same order applies hereinafter), 1727 subjects who received the study drug (874 and 853 subjects) were included in the safety analysis set. Among them, those with efficacy evaluation data at baseline and at ≥1 time point after baseline were included in the evaluable efficacy set (EES).[22)] The study was discontinued in 404 subjects (173 and 231 subjects), and the main reasons for discontinuation were withdrawal by the subject in 205 subjects (94 and 111 subjects) and adverse events in 71 subjects (21 and 50 subjects). In the donanemab group, 69.2% of the subjects (429 of 620 subjects) met the criteria for switching to placebo by Week 76.

Table 14 shows efficacy data in terms of the change in the integrated Alzheimer's Disease Rating Scale (iADRS) score[23)] from baseline to Week 76 of the study treatment, which was the primary endpoint. The superiority of donanemab over placebo in attenuating the decline in the iADRS score was demonstrated both in the overall population (EES) defined as the primary analysis population for the primary endpoint and the population with mild or moderate brain tau accumulation (EES).

Table 14. Change in the iADRS score from baseline to Week 76 of the study treatment (EES)

	Overall population		Population with mild or moderate brain tau accumulation	
	Placebo	Donanemab	Placebo	Donanemab
Baseline[a]	103.82 ± 13.88 (N = 824)	104.55 ± 13.90 (N = 775)	105.95 ± 13.42 (N = 560)	105.92 ± 13.72 (N = 533)
Week 76[a]	93.82 ± 20.38 (N = 653)	96.98 ± 20.87 (N = 583)	98.88 ± 17.95 (N = 444)	101.31 ± 18.23 (N = 418)
Change from baseline (NCS2)[b, c]	−13.11 ± 0.50	−10.19 ± 0.53	−9.27 ± 0.49	−6.02 ± 0.50
Intergroup difference [2-sided 95% CI][b]	-	2.92 [1.508, 4.331]	-	3.25 [1.883, 4.618]
P value for intergroup comparison[b, d]	-	<0.001	-	<0.001

a: Mean ± standard deviation.
b: The NCS2 model included NCS basis expansion term (2 terms), NCS basis expansion term (2 terms)-by-treatment interaction, age at baseline, pooled site, brain tau accumulation at baseline (mild or moderate vs. severe), and use (yes vs. no) of treatment drugs for AD symptoms at baseline (ChE inhibitor and/or memantine) as fixed effects. In the analysis of the population with mild or moderate brain tau accumulation, brain tau accumulation at baseline was excluded from the model. An unstructured variance-covariance matrix was used for the within-subject effect.
c: Least squares mean ± standard error.
d: In consideration of multiplicity in the evaluation using 2 populations, the significance level of intergroup comparison was set at 0.01 (2-sided) for the overall population and 0.04 (2-sided) for the population with mild or moderate brain tau accumulation.

Table 15 shows changes in the Clinical Dementia Rating-Sum of Boxes (CDR-SB), Alzheimer's Disease Assessment Scale-13-item cognitive subscale (ADAS-Cog13), Alzheimer's Disease Cooperative Study-Activities of Daily Living Inventory, instrumental items (ADCS-iADL), and MMSE scores from baseline to Week 76 of the study treatment, while Table 16 shows the change in brain Aβ accumulation based on the amyloid PET Centiloid scale from baseline to Week 76 of the study treatment, which were assessed as secondary endpoints.

22) The number of subjects included in the EES varied by endpoint.
23) iADRS score = [−1 (ADAS-Cog13) + 85] + ADCS-iADL (*J Prev Alzheimers Dis*. 2015;2:227-241). If either ADAS-Cog13 or ADCS-iADL is missing, iADRS is handled as missing.

Table 15. Changes in CDR-SB, ADAS-Cog13, ADCS-iADL, and MMSE scores from baseline to Week 76 of the study treatment (EES)

		Overall population		Population with mild or moderate brain tau accumulation	
		Placebo	Donanemab	Placebo	Donanemab
CDR-SB[e]	Baseline[a]	3.89 ± 2.034 (N = 838)	3.92 ± 2.055 (N = 794)	3.64 ± 1.986 (N = 569)	3.72 ± 2.088 (N = 546)
	Week 76[a]	5.80 ± 3.223 (N = 672)	5.25 ± 3.207 (N = 598)	5.13 ± 2.929 (N = 459)	4.64 ± 2.903 (N = 424)
	Change from baseline (MMRM)[b, c]	2.42 ± 0.092	1.72 ± 0.096	1.88 ± 0.102	1.20 ± 0.105
	Intergroup difference [2-sided 95% CI]	-	−0.70 [−0.95, −0.45]	-	−0.67 [−0.95, −0.40]
ADAS-Cog13[e]	Baseline[a]	29.16 ± 8.85 (N = 841)	28.53 ± 8.78 (N = 797)	27.60 ± 8.21 (N = 570)	27.41 ± 8.44 (N = 550)
	Week 76[a]	34.53 ± 12.00 (N = 677)	32.72 ± 12.44 (N = 607)	31.17 ± 10.37 (N = 460)	29.77 ± 10.65 (N = 431)
	Change from baseline (NCS2)[c, d]	6.79 ± 0.27	5.46 ± 0.28	4.69 ± 0.26	3.17 ± 0.27
	Intergroup difference [2-sided 95% CI]	-	−1.33 [−2.086, −0.565]	-	−1.52 [−2.250, −0.794]
ADCS-iADL[e]	Baseline[a]	47.98 ± 7.70 (N = 826)	47.96 ± 7.85 (N = 780)	48.56 ± 7.70 (N = 562)	48.20 ± 7.88 (N = 535)
	Week 76[a]	43.30 ± 10.61 (N = 661)	44.53 ± 11.06 (N = 591)	45.10 ± 9.82 (N = 451)	46.12 ± 10.26 (N = 420)
	Change from baseline (NCS2)[c, d]	−6.13 ± 0.30	−4.42 ± 0.32	−4.59 ± 0.32	−2.76 ± 0.34
	Intergroup difference [2-sided 95% CI]	-	1.70 [0.840, 2.566]	-	1.83 [0.913, 2.748]
MMSE[e]	Baseline[a]	22.20 ± 3.90 (N = 841)	22.52 ± 3.84 (N = 796)	22.88 ± 3.74 (N = 573)	23.11 ± 3.64 (N = 549)
	Week 76[a]	19.79 ± 5.51 (N = 679)	20.71 ± 5.52 (N = 600)	21.30 ± 4.82 (N = 465)	22.00 ± 4.90 (N = 429)
	Change from baseline (NCS2)[c, d]	−2.94 ± 0.13	−2.47 ± 0.14	−2.09 ± 0.14	−1.61 ± 0.14
	Intergroup difference [2-sided 95% CI]	-	0.47 [0.104, 0.841]	-	0.48 [0.089, 0.868]

a: Mean ± standard deviation.

b: MMRM included treatment group, time point, treatment group-by-time point interaction, baseline value, baseline value-by-time point interaction, age at baseline, pooled site, brain tau accumulation at baseline (mild or moderate vs. severe), and use (yes vs. no) of treatment drugs for AD symptoms at baseline (ChE inhibitor and/or memantine) as fixed effects. In the analysis of the population with mild or moderate brain tau accumulation, brain tau accumulation at baseline was excluded from the model. An unstructured variance-covariance matrix was used for the within-subject effect.

c: Least squares mean ± standard error.

d: The NCS2 model included NCS basis expansion term (2 terms), NCS basis expansion term (2 terms)-by-treatment interaction, age at baseline, pooled site, brain tau accumulation at baseline (mild or moderate vs. severe), and use (yes vs. no) of treatment drugs for AD symptoms at baseline (ChE inhibitor and/or memantine) as fixed effects. In the analysis of the population with mild or moderate brain tau accumulation, brain tau accumulation at baseline was excluded from the model. An unstructured variance-covariance matrix was used for the within-subject effect.

e: Missing data of the subscales of CDR-SB, ADAS-Cog13, ADCS-iADL, and MMSE were handled as follows:
For CDR-SB, if 1 of the 6 items was missing, the total score of the 5 non-missing items was weighted so that the sum would be the maximum of the full CDR-SB score; if ≥2 items were missing, CDR-SB was handled as missing. For ADAS-Cog13, if ≤4 of the 13 items were missing, the total score of the non-missing items was weighted so that the sum would be a maximum of 85 points (full score) for ADAS-Cog13; if ≥5 items were missing, ADAS-Cog13 was handled as missing. For ADCS-iADL, if <30% of the items were missing, the total score of the non-missing items was weighted so that the sum would be the maximum of the full ADCS-iADL score, as above; if >30% of the items were missing, ADCS-iADL was handled as missing. For MMSE, if any of the items were missing, MMSE was handled as missing.

Table 16. Change in brain Aβ accumulation based on the amyloid PET Centiloid scale from baseline to Week 76 of the study treatment (EES)

	Overall population		Population with mild or moderate brain tau accumulation	
	Placebo	Donanemab	Placebo	Donanemab
Baseline[a]	101.75 ± 34.371 (N = 812)	104.02 ± 34.417 (N = 765)	100.94 ± 35.264 (N = 556)	103.00 ± 34.800 (N = 525)
Week 76[a]	101.78 ± 35.710 (N = 690)	14.95 ± 22.820 (N = 614)	101.58 ± 36.548 (N = 470)	13.36 ± 22.375 (N = 433)
Change from baseline (MMRM)[b, c]	−0.67 ± 0.909	−87.03 ± 0.950	0.18 ± 1.065	−88.03 ± 1.104
Intergroup difference [2-sided 95% CI]	-	−86.37 [−88.87, −83.87]	-	−88.21 [−91.22, −85.20]

a: Mean ± standard deviation.
b: MMRM included treatment group, time point, treatment-by-time point interaction, baseline value, baseline value-by-time point interaction, age at baseline, and brain tau accumulation at baseline (mild or moderate vs. severe) as fixed effects. In the analysis of the population with mild or moderate brain tau accumulation, brain tau accumulation at baseline was excluded from the model. An unstructured variance-covariance matrix was used for the within-subject effect.
c: Least squares mean ± standard error.

The safety results are as follows: The incidence of adverse events was 82.2% (718 of 874 subjects) in the placebo group and 89.0% (759 of 853 subjects) in the donanemab group. Table 17 shows adverse events that occurred in ≥5% of subjects in either group.

Table 17. Adverse events that occurred in ≥5% of subjects in either group (safety analysis set, overall population)

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

% (n)

Death was observed in 1.1% of subjects (10 of 874 subjects) in the placebo group (pneumonia in 2 subjects, and myocardial infarction, respiratory failure, sepsis, completed suicide/carbon monoxide poisoning, death, respiratory fume inhalation disorder, dementia Alzheimer's type, and arteriosclerosis in 1 subject each), and 1.9% of subjects (16 of 853 subjects) in the donanemab group (death in 3 subjects, pulmonary embolism and completed suicide in 2 subjects each, and retroperitoneal haemorrhage, COVID-19, subarachnoid haemorrhage, dementia Alzheimer's type, COVID-19 pneumonia, respiratory arrest, amyloid related imaging abnormality-microhaemorrhages and haemosiderin deposits, dehydration, and amyloid related imaging abnormality-oedema/effusion in 1 subject each). Of them, arteriosclerosis in the placebo group, and death in 1 subject in the donanemab group, amyloid related imaging abnormality-microhaemorrhages and haemosiderin deposits, and amyloid related imaging abnormality-oedema/effusion in the donanemab group were assessed as related to the study drug. Serious adverse events were observed in 15.8% of subjects (138 of 874 subjects) in the placebo group and 17.4% of subjects (148 of 853 subjects) in the donanemab group. Events that occurred in ≥1% of subjects in either group were amyloid related imaging abnormality-oedema/effusion (0% in the placebo

group and 1.5% in the donanemab group; the same order applies hereinafter), syncope (1.5% and 1.1%), and COVID-19 (0.5% and 1.1%). Of them, all cases of amyloid related imaging abnormality-oedema/effusion in the placebo group and syncope in 1 subject in the donanemab group were assessed as related to the study drug.

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

Japanese population

Among 88 Japanese patients who were randomized and received the study drug (43 subjects in the placebo group and 45 subjects in the donanemab group; the same order applies hereinafter), the study was discontinued in 14 subjects (7 subjects and 7 subjects), and the main reasons for discontinuation were withdrawal by the subject in 7 subjects (2 subjects and 5 subjects) and adverse events in 4 subjects (3 subjects and 1 subject).

Table 18 shows efficacy data in terms of the change in the iADRS score from baseline to Week 76 of the study treatment, which was assessed as the primary endpoint.

Table 18. Change in the iADRS score from baseline to Week 76 of the study treatment (EES, Japanese population)

	Overall population		Population with mild or moderate brain tau accumulation	
	Placebo	Donanemab	Placebo	Donanemab
Baseline[a]	100.52 ± 12.84 (N = 42)	103.09 ± 10.77 (N = 43)	102.17 ± 13.03 (N = 35)	102.47 ± 10.86 (N = 38)
Week 76[a]	90.94 ± 14.10 (N = 36)	98.80 ± 14.22 (N = 35)	93.27 ± 14.02 (N = 30)	98.75 ± 14.66 (N = 32)
Change from baseline (NCS2)[b, c]	−11.42 ± 1.62	−6.99 ± 1.62	−9.94 ± 1.78	−5.94 ± 1.71
Intergroup difference [2-sided 95% CI]	-	4.43 [−0.173, 9.031]	-	3.99 [−0.978, 8.966]

a: Mean ± standard deviation.
b: The NCS2 model included NCS basis expansion term (2 terms), NCS basis expansion term (2 terms)-by-treatment interaction, age at baseline, pooled site, brain tau accumulation at baseline (mild or moderate vs. severe), and use (yes vs. no) of treatment drugs for AD symptoms at baseline (ChE inhibitor and/or memantine) as fixed effects. In the analysis of the population with mild or moderate brain tau accumulation, brain tau accumulation at baseline was excluded from the model. An unstructured variance-covariance matrix was used for the within-subject effect.
c: Least squares mean ± standard error.

Table 19 show changes in CDR-SB, ADAS-Cog13, ADCS-iADL, and MMSE scores from baseline to Week 76 of the study treatment, while Table 20 shows the change in brain Aβ accumulation based on the amyloid PET Centiloid scale from baseline to Week 76 of the study treatment, which were assessed as secondary endpoints.

Table 19. Changes in CDR-SB, ADAS-Cog13, ADCS-iADL, and MMSE scores from baseline to Week 76 of the study treatment (EES, Japanese population)

		Overall population		Population with mild or moderate brain tau accumulation	
		Placebo	Donanemab	Placebo	Donanemab
CDR-SB[e]	Baseline[a]	3.80 ± 2.223 (N = 42)	3.59 ± 1.695 (N = 43)	3.51 ± 2.215 (N = 35)	3.59 ± 1.720 (N = 38)
	Week 76[a]	5.49 ± 3.190 (N = 36)	4.76 ± 2.840 (N = 36)	4.78 ± 2.824 (N = 30)	4.52 ± 2.690 (N = 32)
	Change from baseline (MMRM)[b, c]	1.64 ± 0.422	1.40 ± 0.430	1.14 ± 0.407	1.23 ± 0.394
	Intergroup difference [2-sided 95% CI]	-	−0.23 [−1.33, 0.87]	-	0.08 [−1.03, 1.20]
ADAS-Cog13[e]	Baseline[a]	29.98 ± 7.43 (N = 43)	29.75 ± 6.21 (N = 44)	29.03 ± 7.40 (N = 36)	29.85 ± 6.15 (N = 39)
	Week 76[a]	35.25 ± 8.77 (N = 36)	31.78 ± 6.92 (N = 36)	33.43 ± 8.45 (N = 30)	31.42 ± 6.95 (N = 33)
	Change from baseline (NCS2)[c, d]	5.40 ± 0.80	2.68 ± 0.80	3.90 ± 0.80	2.38 ± 0.76
	Intergroup difference [2-sided 95% CI]	-	−2.71 [−4.969, −0.458]	-	−1.52 [−3.716, 0.673]
ADCS-iADL[e]	Baseline[a]	45.57 ± 7.90 (N = 42)	47.91 ± 6.76 (N = 43)	46.26 ± 7.36 (N = 35)	47.39 ± 6.93 (N = 38)
	Week 76[a]	41.19 ± 8.21 (N = 36)	45.14 ± 10.57 (N = 36)	41.70 ± 8.45 (N = 30)	45.16 ± 10.73 (N = 32)
	Change from baseline (NCS2)[c, d]	−4.60 ± 1.32	−3.37 ± 1.31	−4.67 ± 1.47	−3.12 ± 1.42
	Intergroup difference [2-sided 95% CI]	-	1.24 [−2.442, 4.913]	-	1.54 [−2.545, 5.631]
MMSE[e]	Baseline[a]	22.60 ± 3.01 (N = 43)	22.86 ± 2.83 (N = 44)	22.92 ± 3.04 (N = 36)	22.90 ± 2.89 (N = 39)
	Week 76[a]	20.36 ± 3.79 (N = 36)	21.47 ± 3.05 (N = 36)	21.37 ± 3.17 (N = 30)	21.76 ± 2.93 (N = 33)
	Change from baseline (NCS2)[c, d]	−2.84 ± 0.45	−1.76 ± 0.45	−2.11 ± 0.48	−1.56 ± 0.46
	Intergroup difference [2-sided 95% CI]	-	1.08 [−0.184, 2.350]	-	0.55 [−0.773, 1.872]

a: Mean ± standard deviation.

b: MMRM included treatment group, time point, treatment-by-time point interaction, baseline value, baseline value-by-time point interaction, age at baseline, pooled site, brain tau accumulation at baseline (mild or moderate vs. severe), and use (yes vs. no) of treatment drugs for AD symptoms at baseline (ChE inhibitor and/or memantine) as fixed effects. In the analysis of the population with mild or moderate brain tau accumulation, brain tau accumulation at baseline was excluded from the model. An unstructured variance-covariance matrix was used for the within-subject effect.

c: Least squares mean ± standard error.

d: The NCS2 model included NCS basis expansion term (2 terms), NCS basis expansion term (2 terms)-by-treatment interaction, age at baseline, pooled site, brain tau accumulation at baseline (mild or moderate vs. severe), and use (yes vs. no) of treatment drugs for AD symptoms at baseline (ChE inhibitor and/or memantine) as fixed effects. In the analysis of the population with mild or moderate brain tau accumulation, brain tau accumulation at baseline was excluded from the model. An unstructured variance-covariance matrix was used for the within-subject effect.

e: Missing data of the subscales of CDR-SB, ADAS-Cog13, ADCS-iADL, and MMSE were handled as follows:
For CDR-SB, if 1 of the 6 items was missing, the total score of the non-missing 5 items was weighted so that the sum would be the maximum of the full CDR-SB score; if ≥2 items were missing, CDR-SB was handled as missing. For ADAS-Cog13, if ≤4 of the 13 items were missing, the total score of the non-missing items was weighted so that the sum would be a maximum of 85 points (full score) for ADAS-Cog13; if ≥5 items were missing, ADAS-Cog13 was handled as missing. For ADCS-iADL, if <30% of the items were missing, the total score of the non-missing items was weighted so that the sum would be the maximum of the full ADCS-iADL score, as above; if >30% of the items were missing, ADCS-iADL was handled as missing. For MMSE, if any of the items were missing, MMSE was handled as missing.

Table 20. Change in brain Aβ accumulation based on the amyloid PET Centiloid scale from baseline to Week 76 of the study treatment (EES, Japanese population)

	Overall population		Population with mild or moderate brain tau accumulation	
	Placebo	Donanemab	Placebo	Donanemab
Baseline[a]	85.14 ± 27.868 (N = 40)	82.76 ± 30.770 (N = 43)	87.31 ± 29.802 (N = 33)	82.33 ± 29.680 (N = 38)
Week 76[a]	91.68 ± 33.767 (N = 36)	9.49 ± 22.294 (N = 36)	93.31 ± 35.558 (N = 30)	7.70 ± 22.072 (N = 32)
Change from baseline (MMRM)[b, c]	6.49 ± 3.621	−72.27 ± 3.924	5.07 ± 3.506	−74.91 ± 3.364
Intergroup difference [2-sided 95% CI]	-	−78.76 [−87.54, −69.98]	-	−79.98 [−89.76, −70.20]

a: Mean ± standard deviation.
b: MMRM included treatment group, time point, treatment-by-time point interaction, baseline value, baseline value-by-time point interaction, age at baseline, and brain tau accumulation at baseline (mild or moderate vs. severe) as fixed effects. In the analysis of the population with mild or moderate brain tau accumulation, brain tau accumulation at baseline was excluded from the model. An unstructured variance-covariance matrix was used for the within-subject effect.
c: Least squares mean ± standard error.

The safety results are as follows: The incidence of adverse events was 76.7% (33 of 43 subjects) in the placebo group and 91.1% (41 of 45 subjects) in the donanemab group. Table 21 shows adverse events that occurred in ≥5% of subjects in either group.

Table 21. Adverse events that occurred in ≥5% of subjects in either group (safety analysis set, Japanese population)

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

% (n)

There were no deaths. Serious adverse events were observed in 18.6% of subjects (8 of 43 subjects) in the placebo group and 15.6% of subjects (7 of 45 subjects) in the donanemab group. None of the events occurred in >1 subject in either group.

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

Safety profile of flortaucipir (^{18}F)

In the safety analysis set, the incidence of adverse events within 2 days after administration of flortaucipir (^{18}F) was 2.3% (39 of 1727 subjects) in the overall population and 2.3% (2 of 88 subjects) in the Japanese population. Adverse events observed in ≥2 subjects in either population were amyloid related imaging abnormality-

microhaemorrhages and haemosiderin deposits (5 subjects in the overall population and 0 subjects in the Japanese population; the same order applies hereinafter), superficial siderosis of central nervous system (3 subjects and 0 subjects), amyloid related imaging abnormality-oedema/effusion (2 subjects and 0 subjects), cerebral microhaemorrhage (2 subjects and 0 subjects), and fall (2 subjects and 0 subjects). There were no deaths or serious adverse events other than death in either population.

Among screening failure subjects (2195 subjects in the overall population and 65 subjects in the Japanese population), the incidence of adverse events observed after administration of flortaucipir (^{18}F) was 0.2% (4 of 2195 subjects) in the overall population and 0% (0 of 65 subjects) in the Japanese population. The only adverse event observed in ≥2 subjects in either population was dizziness (2 subjects in the overall population and 0 subjects in the Japanese population). There were no deaths or serious adverse events other than death in either population.

7.R Outline of the review conducted by PMDA

7.R.1 Efficacy

As a result of the review presented below, PMDA has concluded that PET using flortaucipir (^{18}F) showed efficacy in providing useful information to determine the appropriateness of donanemab treatment in early AD patients.

7.R.1.1 Results of efficacy evaluation

The applicant's explanation about the efficacy of flortaucipir (^{18}F) in early AD patients:

The EFF1 and EFF2 of the foreign phase III study (Study A16) consisted of 49 subjects with dementia, 1 subject with MCI, and 14 CN subjects, which covered all Braak stages. For the diagnostic performance of PET using flortaucipir (^{18}F) investigated in the above population, the sensitivity and specificity for detecting subjects with an NFT score of B3 and for detecting subjects with high ADNC levels are presented in Table 12. Both endpoints met the predefined criterion for efficacy evaluation (achievement of both sensitivity and specificity with the lower bound of the 95% CI exceeding 50% for ≥3 out of 5 interpreters). The criterion for efficacy evaluation was set so that the lower bound of the 95% CI for both sensitivity and specificity would exceed 50%, which corresponds to the expected result of random interpretation of PET images. Given that the point estimates for both sensitivity and specificity are required to be ≥70% to meet the criterion with the actual autopsy cases (67 subjects), this criterion was considered appropriate for evaluation of the diagnostic performance.

In view of the following points, there are no differences between Japanese and non-Japanese patients in the images of PET using flortaucipir (^{18}F) or their reading results:

- In the foreign phase I study (Study A01),[12)] the time course of the body distribution of radioactivity and the retention time of radioactivity in each organ were similar in Japanese and non-Japanese subjects on systemic PET images following single intravenous administration of flortaucipir (^{18}F) 370 MBq in healthy subjects (3 Japanese and 6 non-Japanese subjects). In the foreign phase I study (Study A15), the absorbed doses in each organ/tissue were similar in Japanese and non-Japanese subjects [see Section

6.2.2.1].

- In foreign phase III studies of an AD drug (AZES, TZAX [LZAX], and LMDC studies), which enrolled early AD patients, PET using flortaucipir (^{18}F) was performed on 88 Japanese and 662 non-Japanese subjects. When these subjects were stratified into quartiles based on the SUVr calculated from their PET images, the progress pattern of brain tau accumulation did not differ between the populations in any strata.
- In a Japanese clinical study (Study A27),[24] 5 Japanese interpreters who had undergone a training program read the same images as in a foreign phase III study (Study FR01) under blind conditions.[25] The reading results by the Japanese interpreters were highly concordant with the results by the non-Japanese interpreters obtained in Study FR01 and were also highly concordant among the Japanese interpreters.

In view of the above, PET using flortaucipir (^{18}F) is able to detect the presence/absence of brain tau accumulation at a certain level of accuracy in Japanese patients including those with early AD.

In the global phase III study of donanemab in early AD patients with mild to severe brain tau accumulation detected by PET using flortaucipir (^{18}F) (AACI study), a statistically significant attenuation of the decline in the iADRS score from baseline to Week 76 of the study treatment, which was assessed as the primary endpoint, was observed in the donanemab group compared with the placebo group (Table 14). Secondary endpoints including CDR-SB also consistently showed a trend towards a slower decline in the donanemab group than in the placebo group (Table 15). In view of the above results, donanemab was determined to be clinically useful in the study population of the AACI study and was approved for the indication of "to slow the progression of mild cognitive impairment and mild dementia due to Alzheimer's disease" in Japan.

Taken all together, PET using flortaucipir (^{18}F) has shown efficacy in providing useful information to determine the appropriateness of donanemab treatment in early AD patients.

PMDA's view:
In view of the results of Study A16, PET using flortaucipir (^{18}F) is determined to be able to detect the presence/absence of brain tau accumulation at a certain level of accuracy. Taking into account the positioning of information on the localization of NFTs in the brain in the current Japanese and foreign guidelines [see Section 7.R.3], the data presented in the present application has not demonstrated that the efficacy of PET using flortaucipir (^{18}F) is deemed appropriate for use in the diagnosis and progression evaluation of AD; however, in view of the following points, PET using flortaucipir (^{18}F) has shown efficacy in providing useful information to determine the appropriateness of donanemab treatment in early AD patients.

[24] Image data from 60 subjects randomly extracted from Study FR01 [see Footnote 24] were read by 5 Japanese interpreters who had undergone a training program, in accordance with the criteria for interpretation shown in Table 11. Concordance between these results and those by non-Japanese interpreters in Study FR01 and concordance of the reading results among the Japanese interpreters were evaluated.
[25] Image data of a total of 262 subjects, including autopsy cases, in Study A16 were read by 5 different interpreters from those in Study A16, in accordance with the criteria for interpretation shown in Table 11. The diagnostic performance of PET using flortaucipir (^{18}F) based on the evaluation criteria shown in Table 10 and concordance of the reading results among the interpreters were evaluated.

- The results of Studies A01,[12] A15, and A27[24] suggest no significant intrinsic or extrinsic ethnic factors in the assessment of the presence/absence of brain tau accumulation by PET using flortaucipir (^{18}F), and the effect of donanemab to attenuate the worsening of cognitive function in the Japanese population showed a similar trend to that in the overall population in the AACI study that enrolled patients based also on the results of PET using flortaucipir (^{18}F).
- The approval review of donanemab concluded that donanemab is recommended for a patient population in whom the risk-benefit balance has been clarified based on clinical study results, as seen in the AACI study population, and it is desirable to perform PET using flortaucipir (^{18}F) in advance and then administer donanemab to early AD patients with brain tau accumulation (Review Report of Kisunla Intravenous Infusion 350 mg dated September 3, 2024).

7.R.1.2 Measures for appropriate image interpretation

PMDA asked the applicant to explain factors leading to reading errors in the interpretation of PET images using flortaucipir (^{18}F) based on clinical study results, and then to explain measures for proper image interpretation in the selection of appropriate patients for donanemab.

The applicant's explanation:
In the foreign phase III study (Study A16), the concordance rate between the majority reads of PET images using flortaucipir (^{18}F) by 5 interpreters and the neuropathological findings was assessed as a secondary endpoint. Given the information on cases with discordant results between the reading results and the neuropathological findings in this investigation, the main factor leading to reading errors was that sporadic small areas with visible flortaucipir (^{18}F) accumulation were assessed as tau accumulation, and reading errors frequently tended to occur especially in cases where such sporadic accumulation areas were located mainly in the temporal cortex. Therefore, for proper interpretation of PET images using flortaucipir (^{18}F), it is important to caution that the image interpretation should be based only on the accumulation of flortaucipir (^{18}F) in the cerebral cortex while keeping it in mind that sporadic accumulation may be a false-positive finding.

In view of the above review, the following measures will be taken for the proper interpretation of PET images using flortaucipir (^{18}F) in clinical practice: (a) A training program on the method of image interpretation, including the above precaution, will be provided; and (b) a caution that PET images obtained using flortaucipir (^{18}F) should be read by physicians who have undergone the training program will be included in the package insert.

Concerning the above (a), the training program that is already in use in the US will be translated into Japanese and provided. The content of the training program is the same as that of the program provided to interpreters prior to the AACI study. In Study A27,[24] the reading results by Japanese interpreters who had undergone the program were highly concordant with the results by non-Japanese interpreters [see Section 7.R.1.1]. Taking these into account, the content of the training program provided is considered to be appropriate.

In view of the results of Study A16, PMDA has concluded that measures should be taken for proper assessment of the presence/absence of brain tau accumulation at the time of image interpretation. Therefore, the applicant should provide a training program on the method of image interpretation and should include a cautionary statement in the package insert that the images should be read by physicians who have undergone the training program, to ensure appropriate interpretation based on images obtained using flortaucipir (^{18}F).

7.R.2 Safety

The applicant's explanation about the safety of flortaucipir (^{18}F):

Safety in subjects who received flortaucipir (^{18}F) was investigated in 28 clinical studies shown in Table 22.

Table 22. List of clinical studies included in integrated analysis

Study identifier	Population	Number of enrolled subjects	Dose[a]
Dx studies[b]			
Study T807000	Subjects with high probable AD or low probable AD aged ≥55 years	16	370 MBq
Study A01	Healthy subjects aged ≥20 and ≤40 years, or ≥65 years, and subjects with MCI due to AD or possible/probable AD, aged ≥50 years Subjects who underwent PET using flortaucipir (^{18}F) in Study T807000	36	370 MBq
Study A03	Subjects with probable AD, subjects with MCI, and CN subjects, aged ≥50 years	24	370 MBq
Study A04	Subjects aged ≥50 years who had previously undergone PET using flortaucipir (^{18}F)	44	370 MBq
Study A05	Study A05E: Subjects with AD, subjects with MCI, and CN subjects Study A05C: Subjects with MCI or possible/probable AD	Study A05E: 223 Study A05C: 160	370 MBq
Study A07	Subjects who provided consent to the accompaniment protocol of the study site and were enrolled in the study	41	370 MBq
Study A08	Subjects aged >60 years who met the diagnostic criteria of the AIBL study	86	240 MBq
Study A09	Subjects with PSP, subjects with CBD, and CN subjects, aged 50 to 85 years	29	370 MBq
Study A10	Subjects with probable AD and CN subjects, aged ≥50 years	22	240 MBq
Study A11	Subjects who had participated in ≥10 professional fights	35	370 MBq
Study A13	Subjects aged 60 to 89 years and diagnosed with a life expectancy of ≤6 months	3	370 MBq
Study A14	Subjects with cognitive impairment and CN subjects aged ≥18 years	179	370 MBq
Study A16	Subjects aged ≥50 years and diagnosed with a life expectancy of ≤6 months	156	370 MBq
Study A18	Subjects who completed Study A05C	79	370 MBq
Study A19	FTD patients	14	370 MBq
Study A20	Subjects enrolled in the BIOCARD study	23	370 MBq
BM studies[c]			
TZAX study	Early AD patients who received flortaucipir (^{18}F) in the LZAX study	224	240 MBq
LZBE study[d]	Probable AD patients	9	240 MBq
AZET study[d]	Early AD patients	139	240 MBq
AZES study[d]	Early AD patients	424	240 MBq
AZFD study[d]	Early AD patients		240 MBq
LLCF study[d]	Early AD patients	307	370 MBq
AACG study	Early AD patients	936	370 MBq
LMDC study	Early AD patients	931	370 MBq
Study A23	AD patients	155	370 MBq
Study A24	AD patients	161	370 MBq
ADNI2 study	Subjects with MCI, subjects with SMC, and CN subjects	107	370 MBq
ADNI-DOD study	Subjects with MCI and CN subjects	132	370 MBq

a: Flortaucipir (^{18}F) was administered as a single intravenous dose in all studies.
b: Studies primarily intended to evaluate the diagnostic performance of PET using flortaucipir (^{18}F).
c: Studies using PET with flortaucipir (^{18}F) as a biomarker at study enrollment and during follow-up.
d: Terminated early.

Of 5985 subjects enrolled in the clinical studies, 4652 subjects (including 214 Japanese subjects) who received ≥1 dose of flortaucipir (^{18}F) were included in the safety analysis set. A total of 421 adverse events were observed in 303 subjects (6.5%, 303 of 4652 subjects) in the overall population and 5 adverse events were observed in 4 subjects (1.9%, 4 of 214 subjects) in the Japanese population by 48 hours after administration of

flortaucipir (^{18}F) (by 2 days after administration, if the time of onset was unknown). Table 23 shows adverse events observed in ≥0.2% of subjects in the overall population. In the Japanese population, 5 adverse events were observed in 4 subjects (blood pressure increased and nausea, insomnia, pharyngitis, and skin exfoliation). The severity was mild in 78.6% of events (331 of 421 events), moderate in 18.5% of events (78 of 421 events), and severe in 2.9% of events (12 of 421 events) in the overall population, and all 5 events in the Japanese population were mild.

Table 23. Adverse events that occurred in ≥0.2% of subjects (safety analysis set)

	Overall population (N = 4652)
Headache	0.9 (40)
Injection site pain	0.6 (29)
Diarrhoea	0.3 (13)
Blood pressure increased	0.3 (12)
Dizziness	0.2 (10)
Hypertension	0.2 (8)
Nausea	0.2 (7)

% (n); integrated data from the studies shown in Table 22.

In the overall population, death[26)] was observed in 2 subjects (acute kidney injury and neoplasm malignant in 1 subject each), and a causal relationship to flortaucipir (^{18}F) was ruled out for both events. Serious adverse events other than death were observed in 7 subjects (transient ischaemic attack in 2 subjects, and angina pectoris, myocardial infarction, hand fracture, agitation, and hyperglycaemia in 1 subject each).[27)] Among these, a causal relationship to flortaucipir (^{18}F) was not ruled out for transient ischaemic attack and myocardial infarction (1 subject each), but the sponsor determined that these events were not related to flortaucipir (^{18}F), as described below.

- Transient ischaemic attack (LLCF study): The event may be related to the patient's age (around 75 years), comorbidities (hypertension, hyperlipidemia, diabetes mellitus, etc.) or a smoking history.
- Myocardial infarction (Study A16): The patient was a subject of a study in patients with a terminal illness. The event may be related to comorbidities (hypertension, hypercholesterolemia, and coronary artery disease).

In the Japanese population, there were no deaths or serious adverse events other than death.

In the global phase III study of donanemab (AACI study), the safety in subjects who received flortaucipir (^{18}F) was investigated. In the safety analysis set (1727 subjects in the overall population and 88 subjects in the Japanese population), the incidence of adverse events within 2 days after administration of flortaucipir (^{18}F) was 2.3% (39 of 1727 subjects) in the overall population and 2.3% (2 of 88 subjects) in the Japanese population. Among screening failure subjects (2195 subjects in the overall population and 65 subjects in the Japanese population), the incidence of adverse events observed after administration of flortaucipir (^{18}F) was 0.2% (4 of 2195 subjects) in the overall population and 0% (0 of 65 subjects) in the Japanese population [see Section 7.1.2]. Among the subjects who developed adverse events for 2 days after administration of flortaucipir (^{18}F)

[26)] Deaths that occurred within 7 days after administration of flortaucipir (^{18}F) were classified as treatment-emergent deaths.
[27)] Although the seriousness of hand fracture, agitation, and hyperglycaemia (1 subject each) was not reported by the investigator or subinvestigator, these were handled as serious events due to a lack of information.

in the safety analysis set, 4 adverse events were assessed as related to flortaucipir (^{18}F) in 3 subjects (dizziness and hyperhidrosis, headache, and rash) in the overall population. All of these events were mild in severity and resolved. No adverse events in the Japanese population were assessed as related to flortaucipir (^{18}F). Among the screening failure subjects who developed adverse events after administration of flortaucipir (^{18}F), 8 adverse events were assessed as related to flortaucipir (^{18}F) in 4 subjects (nausea, dizziness, and vomiting; chills, dizziness, and feeling cold; diarrhoea; and paraesthesia) in the overall population. All of these events were mild or moderate in severity and resolved. No adverse events in the Japanese population were assessed as related to flortaucipir (^{18}F).

As described above, there were no particular differences in the incidences of adverse events between Japanese and non-Japanese subjects in the 28 clinical studies shown in Table 22 or the AACI study. Most of the observed adverse events for which a causal relationship with flortaucipir (^{18}F) could not be ruled out were mild or moderate in severity, and the serious adverse events for which a causal relationship with flortaucipir (^{18}F) was not ruled out were also likely influenced by the patient characteristics. Taking these into account, administration of flortaucipir (^{18}F) is unlikely to cause any clinically significant safety concerns.

PMDA has concluded that the applicant's explanation is justified.

7.R.3 Clinical positioning

The applicant's explanation about the clinical positioning of PET using flortaucipir (^{18}F):

The results of the foreign phase III study (Study A16) and other data [see Section 7.R.1.1] demonstrated that PET using flortaucipir (^{18}F) is able to detect the presence/absence of brain tau accumulation at a certain level of accuracy. In foreign countries, the usefulness and appropriate usage of tau PET in the management of AD are recommended (*Alzheimer's Dement*. 2023;19:e078912), and the details, including the target population of tau PET, are the subject of ongoing discussions (*Eur J Nucl Med Mol Imaging*. 2022;49: 895-904). In addition, information on the localization of NFTs in the brain is not recognized as contributing to a confirmed diagnosis of AD in the Japanese management guidelines and related documents. Therefore, there is not medical consensus that obtaining information on the localization of NFTs in the brain provides clear benefits to patients, including the selection of appropriate treatment, based on existing information regarding the management framework of AD. However, in view of the efficacy and safety of flortaucipir (^{18}F) in detecting brain tau accumulation [see Sections 7.R.1 and 7.R.2] as well as the fact that the clinical usefulness of donanemab has been demonstrated in early AD patients with mild to severe brain tau accumulation detected by PET using flortaucipir (^{18}F) in the global phase III study of donanemab (AACI study) [see Section 7.R.1.1], PET using flortaucipir (^{18}F) should be performed for the purpose of obtaining useful information to determine the appropriateness of donanemab treatment in early AD patients.

PMDA has concluded that the applicant's explanation is justified.

7.R.4 Indication

The proposed indication of flortaucipir (^{18}F) was "evaluation of the density and distribution of neurofibrillary tangles in the brain of patients with cognitive impairment suspected of having Alzheimer's disease." However, on the basis of the review in Section 7.R.3, PMDA concluded that the proposed indication does not appropriately reflect the clinical positioning of flortaucipir (^{18}F) and asked the applicant to reconsider the indication of flortaucipir (^{18}F).

The applicant's explanation:

In view of the clinical positioning of flortaucipir (^{18}F), the indication of flortaucipir (^{18}F) will be changed to "to aid in the appropriate use of donanemab (genetical recombination) in patients with mild cognitive impairment or mild dementia due to Alzheimer's disease," and the "Precautions Concerning Indication" section should also include a cautionary statement that, although flortaucipir (^{18}F) is an imaging agent for PET to evaluate the density and distribution of neurofibrillary tangles in the brain, its usefulness in the diagnosis of Alzheimer's disease has not been established.

PMDA's view:

In view of the clinical positioning of flortaucipir (^{18}F), the presented indication of flortaucipir (^{18}F) is justified. Since flortaucipir (^{18}F) is used to obtain information on the presence/absence of brain tau accumulation to determine the appropriateness of donanemab treatment, the statement in the "Precautions Concerning Indication" section should be modified as follows: PET using flortaucipir (^{18}F) should be performed only for the purpose of obtaining information on the presence/absence of brain tau accumulation to determine the appropriateness of donanemab (genetical recombination) treatment. The usefulness of flortaucipir (^{18}F) in the diagnosis of Alzheimer's disease has not been established.

7.R.5 Dosage and administration

The applicant's explanation about the proposed dosage and administration of flortaucipir (^{18}F):

The dose of flortaucipir (^{18}F) was 370 MBq in 21 of the 28 studies conducted using flortaucipir (^{18}F) (Table 22). Therefore, the proposed dose was set as 370 MBq. In the foreign phase II study (Study A10),[28)] the correlation between the SUVr calculated based on PET images and the distribution volume ratio (DVR) estimated using a 2-compartment model was highest at 80 to 100 minutes after administration of flortaucipir (^{18}F), which suggested that the binding of flortaucipir (^{18}F) to the target site is in a near-equilibrium state around that time. Therefore, the start time of PET was set as approximately 80 minutes after administration of flortaucipir (^{18}F). The duration of PET was set as 20 minutes based on the setting in clinical studies conducted with the 370 MBq dose.

In the global phase III study of donanemab (AACI study), tau PET was performed for a longer duration (for 30 minutes starting approximately 75 minutes after administration of flortaucipir (^{18}F)) than the proposed dosage and administration from the perspective of improving the quality of collected data in consideration of

[28)] PET was performed at 40 to 60 minutes, 80 to 100 minutes, or 110 to 130 minutes after administration of flortaucipir (^{18}F).

potential problems such as missing data due to frames with motion. However, tau PET in the AACI study is the same as that specified as the proposed dosage and administration in that the midpoint is 90 minutes after administration of flortaucipir (^{18}F). Therefore, PET at the proposed dosage and administration is considered to produce images equivalent to those obtained in the AACI study.

In view of the above, the dosage and administration of flortaucipir (^{18}F) should include "The dosage is 370 MBq of flortaucipir (^{18}F) administered intravenously, followed by imaging that starts approximately 80 minutes after administration. The duration of imaging is 20 minutes."

On the basis of the reviews on the efficacy and safety of flortaucipir (^{18}F) [see Sections 7.R.1 and 7.R.2] and the applicant's explanation, PMDA has concluded that the presented dosage and administration of flortaucipir (^{18}F) is justified.

7.R.6 Post-marketing investigations

The applicant's explanation about the post-marketing surveillance plan of flortaucipir (^{18}F):
At the time of submission, "false negatives and false positives" were included as an important potential risk in the safety specification of flortaucipir (^{18}F). However, the important point in PET using flortaucipir (^{18}F) performed to obtain useful information to determine the appropriateness of donanemab treatment is to determine whether brain tau accumulation is positive or negative for each patient in the same manner as in the global phase III study of donanemab (AACI study). Although detected signals are not always concordant with the localization of tau, that is not a clinically significant problem. From this perspective, "false negatives and false positives" are not an important potential risk.

Flortaucipir (^{18}F) is filled in vials after adjusting the amount of the drug solution and other parameters in certain ranges to ensure the intended amount of radioactivity at the time of use in consideration of conditions such as the transportation period. If products with a different amount of radioactivity are present at a medical institution, incorrect administration due to mix-ups of products may occur. Taking this into account, "mix-ups of products with a different amount of radioactivity at medical institutions" will be set as an important potential risk, and standard operating procedures to prevent such mix-ups will be prepared as a risk minimization activity for the risk concerned. On the other hand, there are no matters that should be investigated in the post-marketing surveillance concerning "mix-ups of products with a different amount of radioactivity at medical institutions."

In view of the above consideration, no measures such as post-marketing studies are required as additional pharmacovigilance activities at present.

PMDA's view:
The review of safety in subjects who received flortaucipir (^{18}F) [see Section 7.R.2] did not suggest any concerns that should be clarified by conducting post-marketing studies.

For “false negatives and false positives,” in view of the review on measures for appropriate image interpretation [see Section 7.R.1.2], there is concern that reading errors may lead to a situation where patients eligible for donanemab treatment will not be selected appropriately. The training program on the method for interpretation must be properly implemented. Therefore, items related to reading errors should be included as an important potential risk in the safety specification, and then the training program on the method of image interpretation should be implemented as an additional risk minimization activity.

For “mix-ups of products with a different amount of radioactivity at medical institutions” specified as an important potential risk, the presented risk minimization activity is justified.

As a result of the above review, PMDA has concluded that the applicant’s explanation that no measures such as post-marketing studies are required as additional pharmacovigilance activities at present is justified.

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 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.

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

The new drug application data (CTD 5.3.5.1.1) were subjected to an on-site GCP inspection, in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices. On the basis of the inspection, PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted.

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

On the basis of the data submitted, PMDA has concluded that flortaucipir (^{18}F) has efficacy in “aiding in the appropriate use of donanemab (genetical recombination) in patients with mild cognitive impairment or mild dementia due to Alzheimer’s disease,” and that flortaucipir (^{18}F) has acceptable safety in view of its benefits. Providing flortaucipir (^{18}F) to clinical settings as a drug that offers useful information to determine the appropriateness of donanemab treatment in early AD patients is considered to be meaningful.

PMDA has concluded that flortaucipir (^{18}F) may be approved if flortaucipir (^{18}F) is not considered to have any particular problems based on comments from the Expert Discussion.

Review Report (2)

November 12, 2024

Product Submitted for Approval

Brand Name	Tauvid Injection
Non-proprietary Name	Flortaucipir (^{18}F)
Applicant	PDRadiopharma Inc.
Date of Application	April 9, 2024

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).

At the Expert Discussion, the expert advisors supported the PMDA's conclusions concerning the clinical positioning, indication, and dosage and administration of flortaucipir (^{18}F) described in the Review Report (1).

1.1 Efficacy

At the Expert Discussion, the expert advisors supported the PMDA's conclusions, i.e., PET using flortaucipir (^{18}F) has demonstrated its efficacy in terms of the provision of useful information about assessment of eligibility for donanemab treatment in early AD patients, and the obtained images should be read by physicians who have undergone the training program for proper image reading. The expert advisors recommended that the development of image reading training program and the standardization of imaging conditions should be addressed in collaboration with the relevant academic societies prior to the clinical use of flortaucipir (^{18}F).

In view of the expert advisor's comment, PMDA instructed the applicant to work together with the relevant academic societies as necessary for the development of image reading training program, etc. The applicant agreed.

1.2 Safety

At the Expert Discussion, the expert advisors supported the PMDA's conclusion on the unlikeliness of clinically significant safety concerns caused by flortaucipir (^{18}F). However, in actual clinical practice, PET using flortaucipir (^{18}F) is expected to be performed after amyloid PET. From the viewpoint of radiation

exposure, the expert advisors pointed out the need of discussion on whether to set a certain interval between amyloid PET and PET using flortaucipir (^{18}F).

Accordingly, PMDA asked the applicant about their view on the necessity of cautionary advice on the interval between amyloid PET and PET using flortaucipir (^{18}F).

The applicant's explanation:
The anticipated effective doses of PET/CT using flortaucipir (^{18}F) performed following amyloid PET/CT using approved amyloid PET agents (florbetapir [^{18}F]) and flutemetamol [^{18}F]) are 16.88 and 21.00 mSv, respectively,[29)] being below the dose limit for occupational exposure in 1 year in the planned exposure situation (50 mSv, recommendation by the International Commission on Radiological Protection in 2007. Japan Radioisotope Association; 2009. p59-60, etc). Therefore, the radiation dose is considered to be within an acceptable range even when PET/CT using flortaucipir (^{18}F) is performed after amyloid PET/CT.

In the AACI study, amyloid PET/CT and PET/CT using flortaucipir (^{18}F) were performed at screening and Week 76 of donanemab treatment. An interval of ≥16 hours was specified between the 2 scans to preclude any effect of the initially administered PET agent on the images obtained with the subsequent PET/CT. No clinically significant adverse events were observed after the administration of flortaucipir (^{18}F) in the study. In actual clinical practice, flortaucipir (^{18}F) will be ordered only after confirming that the result of the amyloid PET is positive, whereafter PET using flortaucipir (^{18}F) will be performed. Therefore, PET using flortaucipir (^{18}F) is not expected to be performed within 16 hours after amyloid PET.

In view of the above, cautionary advice on the interval between amyloid PET and PET using flortaucipir (^{18}F) is unnecessary.

On the basis of the applicant's explanation, PMDA has concluded that there is no need to provide cautionary advice on the interval between amyloid PET and PET using flortaucipir (^{18}F). The expert advisors supported the PMDA's conclusion.

1.3 Risk management plan (draft)

In view of the review in Section "7.R.6 Post-marketing investigations" of the Review Report (1) and the comments of the expert advisors at the Expert Discussion, PMDA has concluded that the risk management plan (draft) for flortaucipir (^{18}F) should include the safety specification presented in Table 1, and that the applicant should conduct the additional pharmacovigilance activity and risk minimization activities presented in Table 2.

[29)] At assumed doses of florbetapir (^{18}F), flutemetamol (^{18}F), and flortaucipir (^{18}F) as 370 MBq

Table 1. Safety and efficacy specifications in the risk management plan (draft)

Safety specification		
Important identified risks	Important potential risks	Important missing information
• None	• Reading errors • Mix-ups of products with a different amount of radioactivity at medical institutions	• None
Efficacy specification		
• None		

Table 2. Summary of the additional pharmacovigilance activity and risk minimization activities included under the risk management plan (draft)

Additional pharmacovigilance activity	Additional risk minimization activities
• Early post-marketing phase vigilance	• Provision of information collected through early post-marketing phase vigilance • Implementation of image reading training program for physicians • Establishment and appropriate operation of the standard operating procedures for mix-up prevention • Preparation and provision of materials for healthcare professionals (Request for Proper Use)

1.4 Transporter-mediated pharmacokinetic interactions

The applicant's explanation:

Transporter-mediated pharmacokinetic interactions are unlikely to occur in the clinical use of flortaucipir (^{18}F), in view of the investigation results presented in Section "6.2.1.5 Investigation of transporters" of the Review Report (1) and the following investigation results obtained after preparation of the Review Report (1), as well as data including the plasma unbound flortaucipir (^{18}F) concentration[30)] anticipated in the clinical setting.

- When flortaucipir (^{18}F) 0.5 μmol/L was added to MDCK cells engineered to express BCRP, the efflux ratio in the absence of a BCRP inhibitor (Ko143) was similar to that in the presence of the inhibitor, which indicates that flortaucipir (^{18}F) is not a substrate of BCRP.
- When flortaucipir (^{18}F) 0.5, 1, or 5 μmol/L was added to human embryonic kidney cells 293 (HEK293) engineered to express organic anion transporting polypeptide (OATP)1B1, OATP1B3, OAT1, OAT3, OCT2, MATE1, or MATE2-K and to control cells, the intracellular intake of flortaucipir (^{18}F) in the cells expressing these transporters was similar to that in the control cells, which indicates that flortaucipir (^{18}F) is not a substrate of these transporters.
- When each substrate of (a) BCRP, (b) OATP1B1, (c) OATP1B3, (d) OAT1, (e) OAT3, (f) OCT2, (g) MATE1, and (h) MATE2-K[31)] as well as flortaucipir (^{18}F)[32)] were added to HEK293 cells engineered to express the corresponding transporters, the IC_{50} was (a) 0.288 μmol/L, (b) >12.0 μmol/L, (c) >12.0 μmol/L, (d) >9.64 μmol/L, (e) >12.0 μmol/L, (f) 4.62 μmol/L, (g) 2.07 μmol/L, and (h) 0.437 μmol/L, respectively.

PMDA has concluded that the applicant's explanation is justified.

30) Estimated to be 0.00080 μmol/L based on the C_{max} (0.015 μmol/L) and plasma unbound fraction (0.053) of flortaucipir (^{18}F) anticipated in the clinical setting.
31) Compounds used as substrates of the transporters: BCRP, rosuvastatin; OATP1B1/OATP1B3, atorvastatin; OAT1, para-aminohippurate; OAT3, furosemide; OCT2/MATE1//MATE2-K, metformin.
32) Flortaucipir (^{18}F) concentrations used for the investigation of each transporter: BCRP, 0.03 to 20.00 μmol/L; OATP1B1/OATP1B3/OAT1/OAT3/OCT2, 0.0203 to 12.0 μmol/L; MATE1/MATE2-K, 0.0248 to 11.8 μmol/L.

2. 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 below, with the following conditions. Since the product is a drug with a new active ingredient, the re-examination period is 8 years. The product is not classified as a biological product or a specified biological product. Neither the drug product nor its drug substance is classified as a poisonous drug or a powerful drug.

Indication

Aiding in appropriate administration of donanemab (genetical recombination) in patients with mild cognitive impairment or mild dementia due to Alzheimer's disease

Dosage and Administration

The dose is 370 MBq of flortaucipir (^{18}F) administered intravenously. Image acquisition should start approximately 80 minutes after administration. The imaging duration is 20 minutes.

Approval Conditions

1. The applicant is required to develop and appropriately implement a risk management plan.
2. Taking into account the product's characteristics as radiopharmaceutical, the applicant is required to appropriately set manufacturing and quality control testing items for product release decision, and take proper post-marketing measures to ensure appropriate distribution control based on the testing results.

Appendix

List of Abbreviations

Aβ	Amyloid β
AD	Alzheimer's disease
ADAS-Cog13	Alzheimer's disease assessment scale-13-item cognitive subscale
ADCS-iADL	Alzheimer's disease cooperative study-activities of daily living inventory, instrumental items
ADNC	Alzheimer's disease neuropathologic change
AML12	Alpha mouse liver 12
ARIA	Amyloid-related imaging abnormalities
ARIA-E	Amyloid-related imaging abnormalities-edema/effusion
αSYN	α-synuclein
[redacted]	[redacted]
AV-1622	5-[5-(*tert*-butoxycarbonyl)-5*H*-pyrido[4,3-*b*] indol-7-yl]-N,N,N-trimethylpyridin-2-aminium 4-methylbenzenesulfonate
[redacted]	[redacted]
BCRP	Breast cancer resistance protein
CBD	Corticobasal degeneration
CDR-SB	Clinical dementia rating-sum of boxes
ChE	Cholinesterase
CHO cells	Chinese hamster ovary cells
CI	Confidence interval
CL_{int}	Intrinsic clearance
CN	Cognitively normal
COSY	Correlation spectroscopy
COVID-19	Coronavirus disease 2019
CT	Computed tomography
CTE	Chronic traumatic encephalopathy
CYP	Cytochrome P450
DMSO	Dimethyl sulfoxide
DLB	Dementia with Lewy bodies
Donanemab	Donanemab (genetical recombination)
DPM	Disease progression model
DVR	Distribution volume ratio
Early AD	Mild cognitive impairment due to Alzheimer's disease and mild dementia due to Alzheimer's disease
EES	Evaluable efficacy set
EFF	Efficacy analysis set
EOS	End of synthesis
FEH	Fluoroethyl harmol
Flortaucipir (^{18}F)	Flortaucipir (^{18}F)
FTD	Frontotemporal dementia
GC	Gas chromatography
HEK293	Human embryonic kidney cells 293
hERG	human ether-a-go-go related gene
HMBC	Heteronuclear multiple bond coherence
HPLC	High performance liquid chromatography
HSQC	Heteronuclear single quantum correlation
iADRS	Integrated Alzheimer's disease rating scale
IC_{50}	Half maximal inhibitory concentration

ICH M7(R2) guideline	Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk (PSEHB/ELD Notification No. 1110-3 dated November 10, 2015)
IR	Infrared absorption spectroscopy
K_d	Dissociation constant
LC/MS	Liquid chromatography mass spectrometry
LS174T	Laboratory of surgery 174T
MAO	Monoamine oxidase
MATE	Multidrug and toxin extrusion
MCI	Mild cognitive impairment
MCI due to AD	Mild cognitive impairment due to Alzheimer's disease
MDCK	Madin-Darby canine kidney
Memantine	Memantine hydrochloride
MMRM	Mixed model for repeated measures
MMSE	Mini-mental state examination
MRC5	Medical research council cell strain 5
MS	Mass spectrometry
MSA	Multiple system atrophy
NCS	Natural cubic spline
NCS2	Natural cubic spline model with 2 degrees of freedom
NFT	Neurofibrillary tangle
NIA-AA	National institute on aging-Alzheimer's association
NMR	Nuclear magnetic resonance spectroscopy
OAT	Organic anion transporter
OATP	Organic anion transporting polypeptide
OCT	Organic cation transporter
P_{app}	Apparent permeability coefficient
PE	Polyethylene
PET	Positron emission tomography
P-gp	P-glycoprotein
PHF	Paired helical filament
PiD	Pick's disease
PMDA	Pharmaceuticals and Medical Devices Agency
PSP	Progressive supranuclear palsy
[redacted]	[redacted]
SD	Sprague-Dawley
SMC	Subjective memory complaints
SOT	Standard of truth
SUV	Standardized uptake value
SUVr	Standardized uptake value ratio
Tauvid	Tauvid Injection
TDP43	TAR DNA-binding protein 43
TD_{50}	Median toxic dose
TTC	Threshold of toxicological concern
UV/VIS	Ultraviolet-visible spectrophotometry